Asymmetric Jocic Reactions

by

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DECLARATION

All of the work carried out in this thesis is original research work carried out at the University of Warwick between October 2011 and August 2014. I declare that the material described that is not original has been identified and appropriately referenced. I certify that the material within this thesis has not been submitted for a degree at any other university.

Some of this work has appeared in the scientific literature in:

Michael S. Perryman, Matthew E. Harris, Jade L. Foster, Anushka Joshi, Guy J. Clarkson and David J. Fox. *Chem. Commun.*, 2013, **49**, 10022-10024.

ABSTRACT

Jocic reactions involve the reaction of trihalocarbinols with nucleophiles *via* 2,2-dichloroepoxides. Stereospecific versions with enantiomerically enriched trihalocarbinols are however rather uncommon. This is probably due to the very few methods of synthesising enantiomerically enriched trihalocarbinols. This thesis describes the development of a general route for synthesis of enantiomerically enriched trichlorocarbinols and their subsequent use in stereoselective Jocic reactions.

Chapter 1 discusses the work towards developing a general route for the asymmetric transfer hydrogenation of trichloromethyl ketones. Initially a brief overview of stereoselective hydrogenation and the required forms of chelation is given. Following this, a detailed review of the known directing groups for asymmetric transfer hydrogenation reactions is provided before the report of the discovery that the trichloromethyl moiety may also be a strong directing group. Finally, the ability of trichloromethyl as a directing group for transfer hydrogenation reactions is explored.

Chapter 2 opens with a summary of the reported mechanistic investigations into the Jocic reaction. Following this, a detailed review of the different nucleophiles used in both racemic and stereospecific Jocic-type reactions is given. Then, the current reported syntheses of enantiomerically enriched piperazin-2-ones, and related compounds, is discussed. Finally, the development of a general synthesis for these compounds is explored using amine nucleophiles in stereospecific Jocic-type reactions.

Chapter 3 opens with a discussion of a publication which reports the enzymatic resolution of an allylic trichloromethyl acetate for the synthesis of its corresponding alcohol in high enantiomeric excess. Following this, the use of porcine liver esterase and *Candida rugosa* lipase are investigated for enzymatic resolutions with acetate derivatives of some of the trichlorocarbinols from in Chapter 1.

ABBREVIATIONS

Ac	Acetyl
aIle	*allo*-Isoleucine
Anal.	Analysis
atm	Atmospheres
aq.	Aqueous
ATH	Asymmetric transfer hydrogenation
BINAL-H	2,2’-Dihydroxy-1,1’-binapthyl lithium aluminium hydride
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
br.	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
Calc.	Calculated
CBS	Corey-Bakshi-Shibata
CI	Chemical Ionisation
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Config.	Configuration
Cpd	Compound
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
CRL	*Candia rugosa* lipase
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarisation
DIBAL-H	Diisobutylaluminium hydride
dil.	Dilute
DIPEA	Diisopropylethylamine
DFT	Density functional theory
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
d.r.	Diastereomeric ratio
DMSO	Dimethyl sulfoxide
EDCI	3-(Ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine
e.e.	Enantiomeric excess
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FT	Fourier transform
gem	Geminal
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
Glu	Glutamic acid
h	Hour(s)
His	Histidine
HOBt	1-Hydroxybenzotriazole
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronuclear multiple-quantum correlation spectroscopy

HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
i	iso
IBX	2-Iodoxybenzoic acid
Ile	Isoleucine
L	Ligand
LiHMDS	Lithium hexamethyldisilazide
lit.	Literature
LRMS	Low resolution mass spectrometry
Ltd	Limited
m	Multiplet (in ^{1}H NMR assignments), medium (in IR assignments)
M	Molar
Me	Methyl
min.	Minutes
m.p.	Melting point
1-Nap	1-Napthyl
NMR	Nuclear magnetic resonance
non.	Nonet
Nu	Nucleophile
oct.	Octet
PCC	Pyridinium chlorochromate
PFL	*Pseudomonas fluorescens* lipase
PGGTase I	Protein geranylgeranyltransferase-I
Ph	Phenyl
PhD	Doctor of philosophy
PLE	Porcine liver esterase

PPAR	Peroxisome proliferator-activated receptor
PPL	Porcine pancreatic lipase
ppm	Parts per million
Pr	Propyl
PTC	Phase transfer catalyst
q	Quartet
quat.	Quaternary
quin.	Quintet
rac	Racemic
RDS	Rate determining step
rt	Room temperature
s	Singlet (in ^{1}H NMR assignments), sharp (in IR assignments)
sat.	Saturated
S/C	Substrate to catalyst ratio
sept.	Septet
Ser	Serine
sext.	Sextet
t	Triplet
T	Temperature
TBAF	Tetra-*N*-butylammonium fluoride
TBAI	Tetra-*N*-butylammonium iodide
tert	Tertiary
teth	Tethered
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMS	Trimethylsilane
TOF	Time of flight
TS	Transition state
TsDPEN	(±)-*N*-*p*-Tosyl-1,2-diphenylenediamine
UV	Ultraviolet
w	Weak
ZPE	Zero point energy

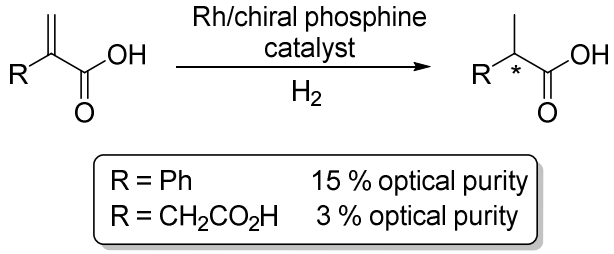
CHAPTER 1 – Asymmetric Transfer Hydrogenation of Trichloromethyl Ketones.

1.1 INTRODUCTION

1.1.1 Hydrogenation.

The 2001 Nobel Prize in Chemistry was awarded to Knowles,[1] Noyori[2] and Sharpless[3] for their contributions in the field of asymmetric catalysis. The half of the prize shared between Knowles and Noyori was for their work on asymmetrically catalysed hydrogenation reactions.[4] Asymmetric hydrogenation reactions are one of the most important processes in synthetic chemistry, particularly in the pharmaceutical industry,[5] and have been extensively researched for over 45 years.

In the late 1950s and early 1960s the development of soluble hydrogenation catalysts really began.[6] The complexes reported by Halpern,[7] Breslow[8] and Wilkinson[9] were amongst the first homogenous catalysts for the hydrogenation of olefins. It was not until 1968 that Knowles and coworkers reported the first homogenous asymmetric catalytic hydrogenation system with α-phenylacrylic acid and 2-methylenesuccininc acid as substrates (Scheme 1).[10]



Scheme 1 First reported homogeneous catalyst for the asymmetric hydrogenation of olefins.

Several developments in this field led to the discoveries of other rhodium complexes using chiral phosphine ligands such methylphenyl-*o*-anisylphosphane (PAMP),[11] methylcyclohexyl-*o*-anisylphosphane (CAMP),[12] (4*S*,5*S*)-2,2-dimethyl-4,5-((diphenyl-phosphino)dimethyl)dioxolane ((*S*,*S*)-DIOP),[13] (1*S*,2*S*)-1,2-bis[(2-methoxyphenyl)-

(phenylphosphino)]ethane (DiPAMP), (2*S*,3*S*)-bis(diphenylphosphino)butane ((*S*,*S*)-chiraphos),[14] 1-[1',2-bis(diphenylphosphino)ferrocenyl]-ethyldimethylamine (BPFFA),[15] (2*S*,4*S*)-*N*-butoxycarbonyl-4-diphenlylphosphino-2-diphenylphosphino-methylpyrrolidine ((*S*,*S*)-BPPM),[16] (1*S*,2*S*)-N^1,N^2-bis(diphenylphosphanyl)-1,2-diphenylethane-1,2-diamine ((*S*,*S*)-PNNP)[17] and DuPhos (Figure 1).[18, 19]

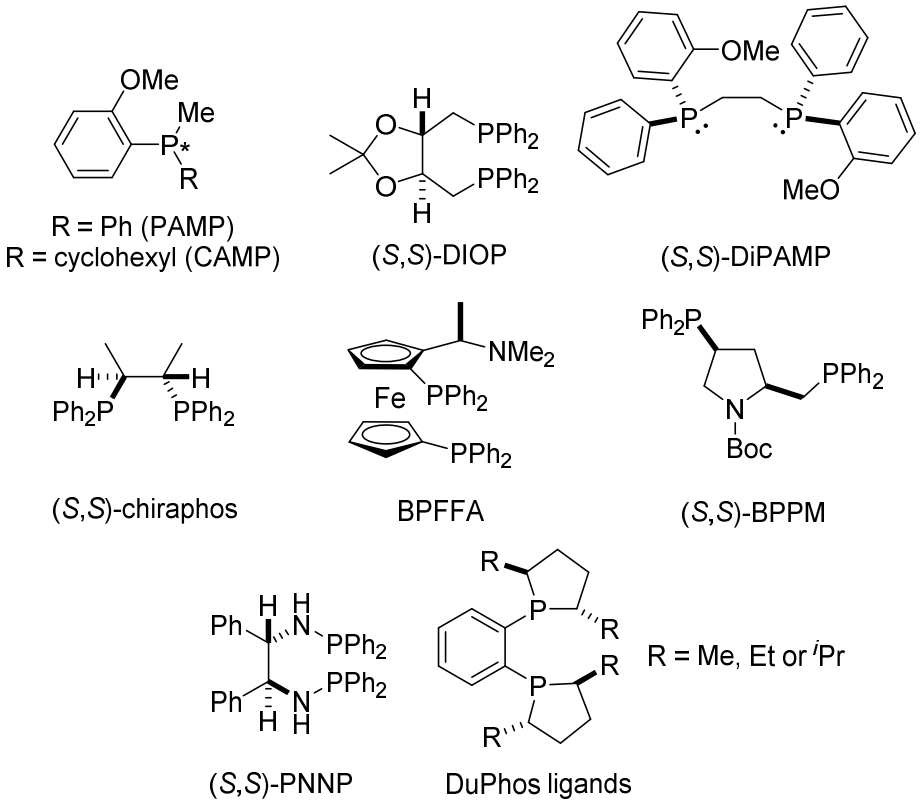


Figure 1 Chiral phosphine ligands used in catalytic asymmetric hydrogenation reactions.

Despite considerable success with the chiral phosphine ligands (Figure 1),[20, 21] the asymmetric hydrogenation of Knowles' original model, α-phenylacrylic acid, did not work.[12] Noyori and coworkers overcame this problem with the discovery of a novel chiral diphosphine ligand, BINAP (Figure 2).[22-30]

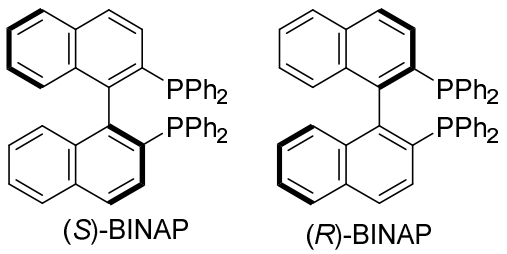


Figure 2 Both enantiomers of the chiral diphosphine ligand BINAP.

Following the success with rhodium(I)/BINAP catalysts[2] Noyori and coworkers reported a far superior ruthenium(II) version.[31-37] It was at this point when the asymmetric reduction of functionalised ketones took off.

1.1.2 Asymmetric Hydrogenation of Functionalised Ketones.

Until the mid-1990s, ruthenium catalysed asymmetric hydrogenations of prochiral ketones required the presence of a chelating group to interact with the metal centre.[2] Amongst the first catalysts for the asymmetric pressure hydrogenation of functionalised ketones was Noyori's ruthenium(II)/BINAP system.[38-41] The chelating groups required for the successful asymmetric hydrogenations using this system included dialkylamino, hydroxyl, alkoxycarbonyl, alkylamido and alkylthiocarbonyl (Figure 3).[42]

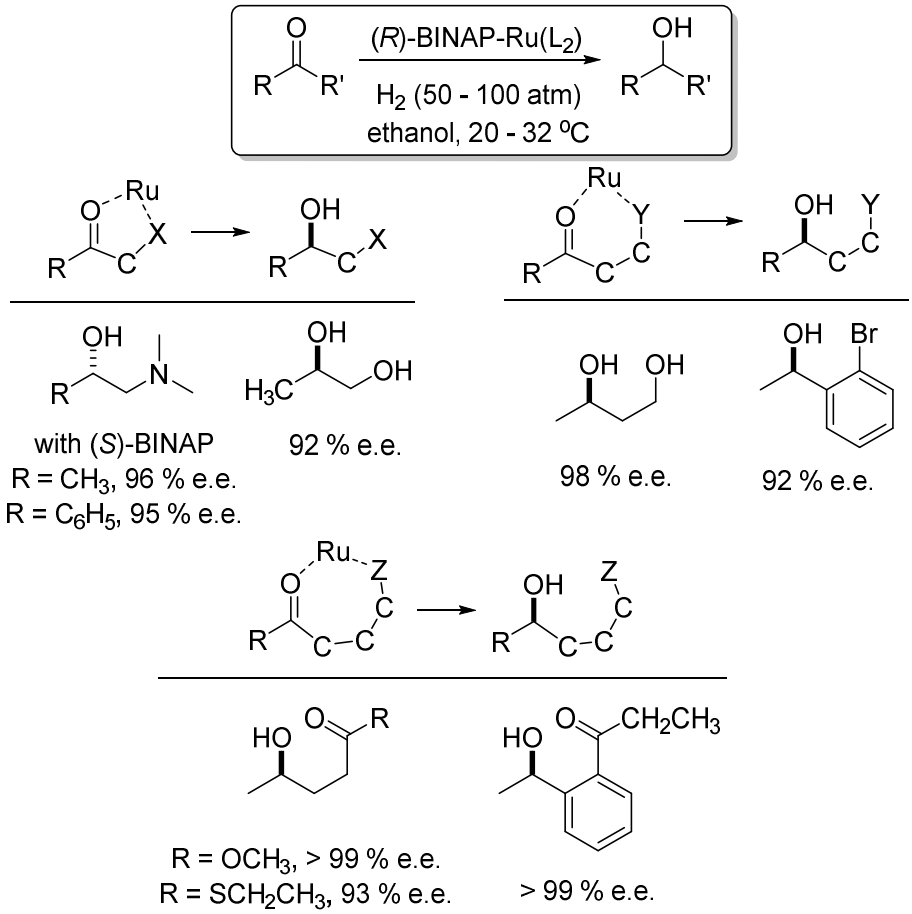


Figure 3 Asymmetric hydrogenation of prochiral ketones containing a chelating group using (*R*)- and (*S*)-BINAP.

It was suggested that the diastereomeric intermediates formed in the reaction were five- to seven-membered chelate complexes (Figure 3).[42] Interestingly, unsubstituted acetophenone and *m*- or *p*-bromoacetophenone were hydrogenated in less than 1 % yield and in only moderate enantiomeric excesses (Figure 4) with opposite enantioselection compared with the reduction of *o*-bromoacetophenone.[43] This suggested that suitably positioned halogen atoms can control the enantiofacial selectivity of the reaction through coordination to the ruthenium centre.[43]

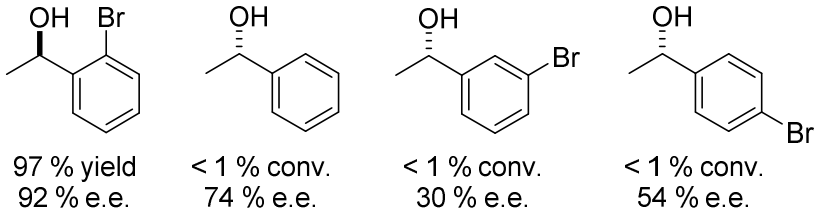
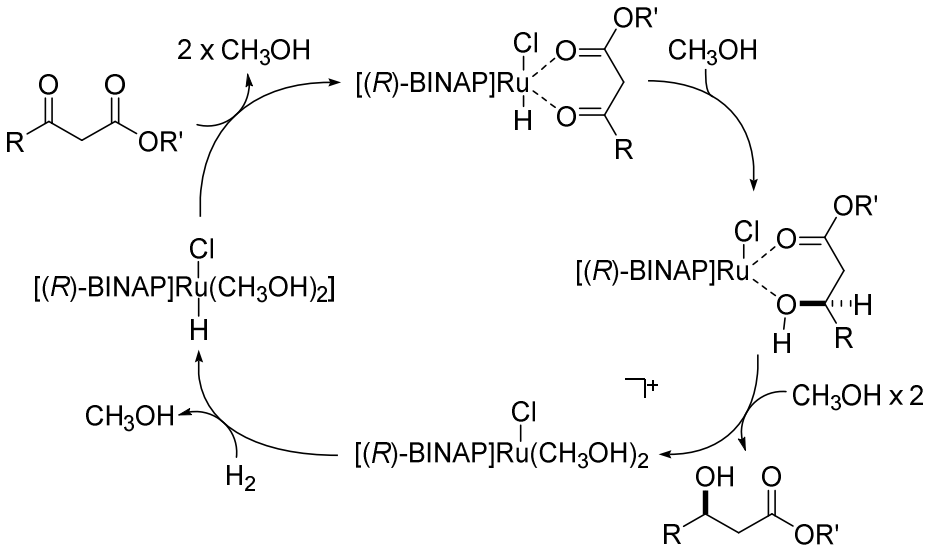


Figure 4 Asymmetric hydrogenation of 2'-bromoacetophenone and unactivated acetophenone and derivatives with (*R*)-BINAP.

The extensive research into this catalyst system enabled the successful asymmetric reduction of a variety of functionalised ketones to their corresponding alcohols in 90-100 % enantiomeric excesses.[2, 41, 44, 45] Scheme 2 demonstrates the proposed mechanism for the ruthenium(II) catalysed asymmetric hydrogenation of β-keto esters to their corresponding enantiomerically enriched β-hydroxy esters.[2]



Scheme 2 Catalytic cycle for the BINAP/Ru(II) asymmetric hydrogenation of β-keto esters.

The β-keto ester moiety interacts with the ruthenium complex gives the RuHCl species.[2] This species facilitates the hydride transfer from the ruthenium centre to the carbonyl carbon. In order for there to be high enantioselective discrimination in this step the presence of the ester functionality is absolutely crucial.[41] In the stereodetermining step two diastereomeric chelate complexes are formed of which one is more stable and hence more reactive than the other. The two diastereomeric complexes are shown in Figure 5.

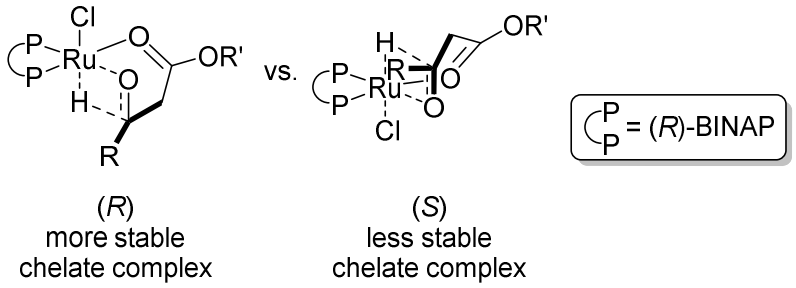


Figure 5 Two diastereomeric transition state complexes for the reduction of β-keto esters.

The size and stability of the chelate complex depends on the nature of the R group. For example, if there is a competing functional group the enantiomeric excess has been shown to deteriorate. This is highlighted by the examples shown in Figure 6.

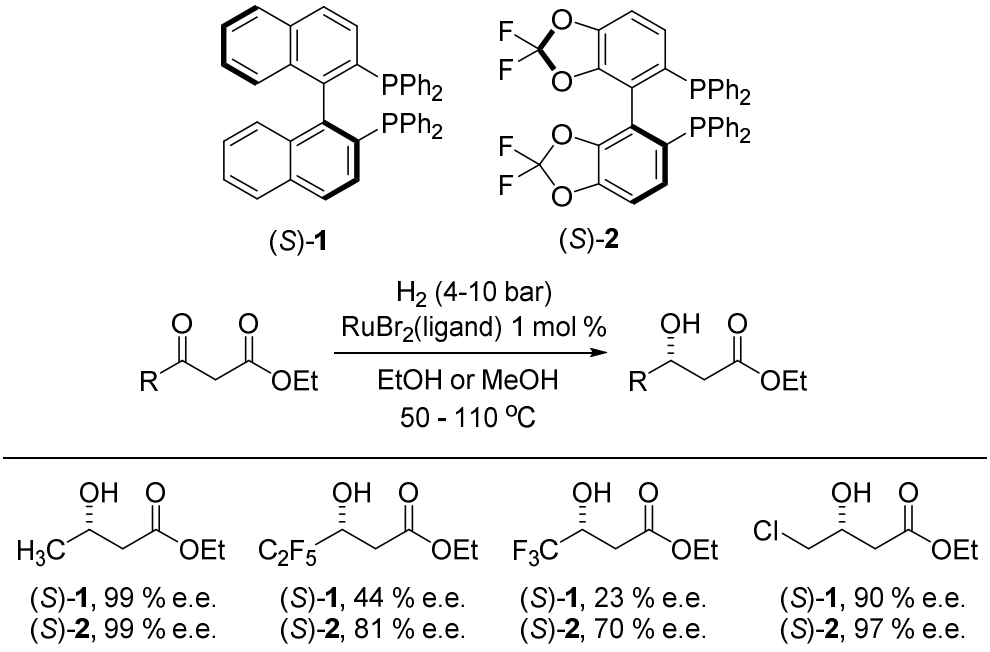


Figure 6 Competing chelating groups for the asymmetric reduction of β-keto esters.

When R^1 is methyl excellent enantiofacial control is maintained for the reduction because a 6-membered chelate complex is formed in the transition state of the stereodetermining step (Figure 5). When the methyl is replaced with the trifluoromethyl group the enantiomeric excess drops significantly, more so when BINAP is used (Figure 6). This is thought to be because of competition between 5- and 6-membered chelate complexes in the transition state of the stereodetermining step (Figure 7).

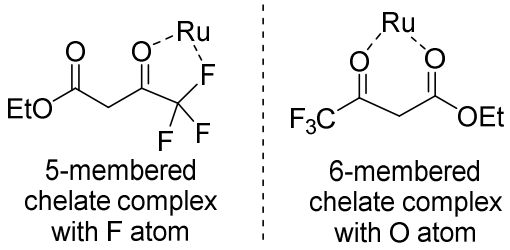
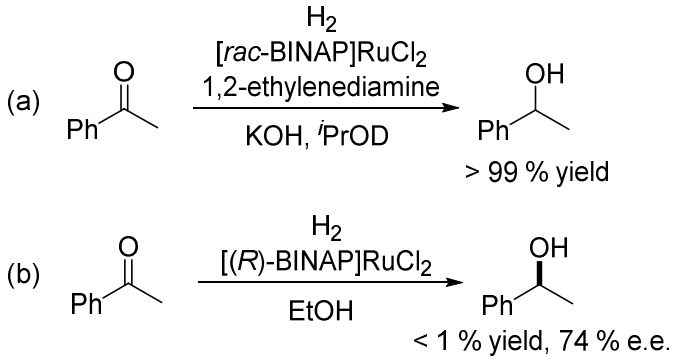


Figure 7 Competing 5- and 6-diastereomeric chelate complexes in the transition state.

Up to this point in time the asymmetric reduction of prochiral ketones required a chelating moiety for high enantioselectivities. Section **1.1.3** discusses the advances made by Noyori and coworkers towards the development of a homogenous catalytic system that could reduce unfunctionalised prochiral ketones with a high degree of enantioselectivity.

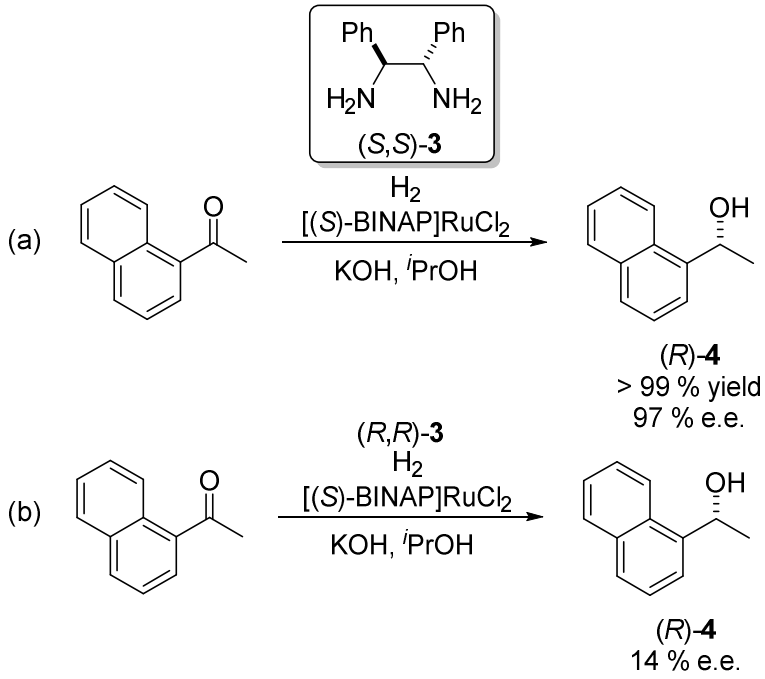
1.1.3 Asymmetric Hydrogenation of Unfunctionalised Prochiral Ketones.

In 1995, Noyori *et al*. reported that the addition of a diamine ligand to the reaction mixture promoted the reduction of previously unreactive systems such as acetophenone and derivatives.[46] The hydrogenation of acetophenone with *rac*-BINAP and 1,2-ethylenediamine with potassium hydroxide and deuterated 2-propanol gave 1-phenylethanol in greater than 99 % yield (a, Scheme 3).[46] This was an enormous advance in the catalytic activity compared with the previously reported conditions (b, Scheme 3).[46]



Scheme 3 Hydrogenation of acetophenone with and without the addition of a diamine.

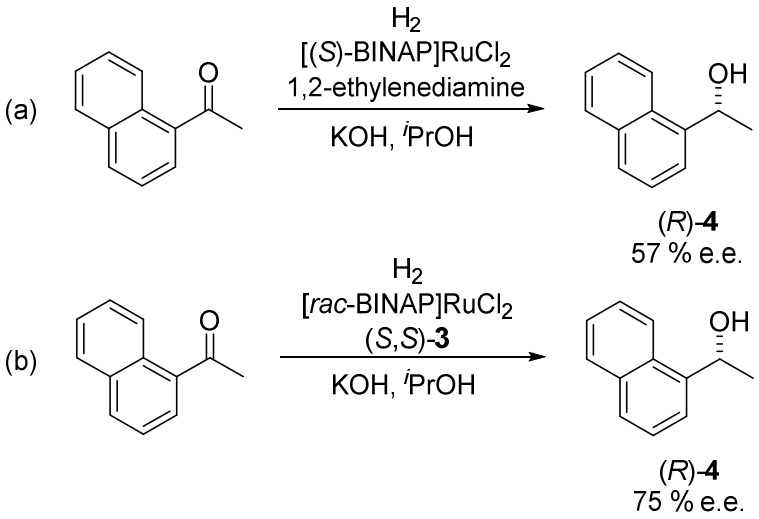
Noyori and coworkers went on to explore the asymmetric version of this more active ruthenium/BINAP/diamine system.[46] The hydrogenation of 1'-acetonaphthone with (*R*)-BINAP and an (*S*,*S*)-1,2-diphenylethylenediamine (*S*,*S*)-**3** derived catalytic system gave (*R*)-1-(1-naphthyl)ethanol (*R*)-**4** in greater than 99 % yield and an excellent 97 % e.e. (a, Scheme 4). Whilst the synergistic effect of (*S*,*S*)-**3** and (*S*)-BINAP led to an increased enantiofacial control, replacement with (*R*,*R*)-**3** gave the desired alcohol in only 14 % e.e. and with the same configuration of product (b, Scheme 4) .[46]



Scheme 4 Hydrogenation of 1-napthyl ketone with ligand (*S*,*S*)-**3** and (*R*,*R*)-**3**.

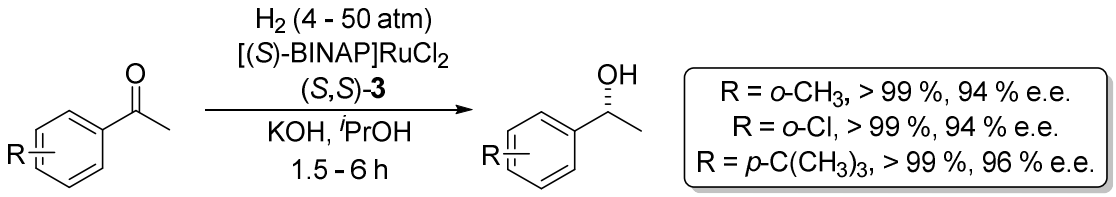
Further investigation into this system involved a combination of (*S*)-BINAP and achiral 1,2-ethylenediamine with otherwise identical conditions, which gave (*R*)-**4** in a

moderate 57 % e.e. (a, Scheme 5).[46] Additionally, using *rac*-BINAP and (*S*,*S*)-**3** gave (*R*)-**4** in 75 % e.e., suggesting that the chiral diamine is playing a more important role than the chiral BINAP in the stereodetermining step of the reaction (b, Scheme 5).[46]



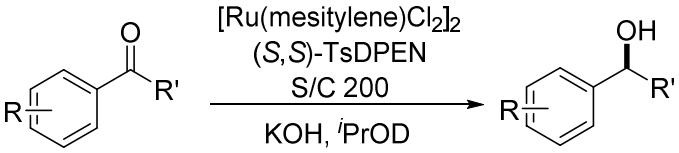
Scheme 5 Hydrogenations of 1-napthyl ketones with BINAP ligands and diamines.

Using this newly developed ruthenium(II)/BINAP/diamine/inorganic base catalytic system Noyori and coworkers showed that a variety of 'unactivated' prochiral ketones could be hydrogenated in high enantiomeric excesses.[46] The hydrogenation of 'non-chelating' *o*-methylacetophenone and *p-tert*-butylacetophenone as well as 'chelating' *o*-chloroacetophenone are shown in Scheme 6.[46]



Scheme 6 Hydrogenation of substituted-acetophenones.

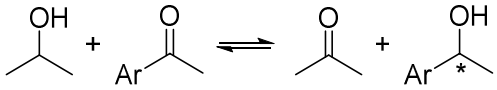
Shortly after, Noyori *et al*. discovered a more active catalytic system for the asymmetric transfer hydrogenation of prochiral ketones compared with those previously reported.[46-49] This new system used 2-propanol as the hydrogen donor and facilitated the asymmetric hydrogenation of a variety of prochiral ketones in excellent enantiomeric excess (Table 1).



R	R'	Time	Yield %	e.e. % (config.)
H	Me	15	95	97 (*S*)
H	Et	14	94	97 (*S*)
o-Me	Me	24	53	91 (*S*)
m-Cl	Me	2.5	98	98 (*S*)
p-Cl	Me	19	95	93 (*S*)
m-OMe	Me	16	96	96 (*S*)
p-OMe	Me	20	53	72 (*S*)

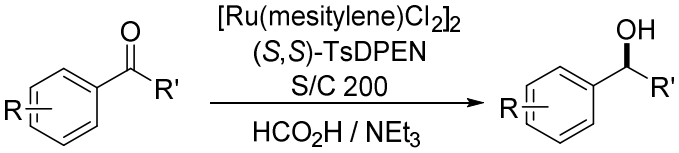
Table 1 2-Propanol as a hydrogen donor in asymmetric transfer hydrogenations.

There are some chemical problems associated with using 2-propanol as a hydrogen donor for the asymmetric transfer hydrogenation of prochiral substrates.[50] Even if the reaction proceeds with excellent enantiofacial selectivity the enantiopurity of the chiral product can frequently deteriorate.[50] As both the hydrogen donor and product are secondary alcohols there is a risk of reaction reversibility and product racemisation (Scheme 7).



Scheme 7 Reversibility issues with using 2-propanol as the hydrogen donor.

The use of triethylammonium formate[51] would remove the reversibility issue, since carbon dioxide is generated in the 'hydrogen-forming' step, and would theoretically allow the reactions to proceed with 100 % conversion and complete enantioselection.[50] In 1996, Noyori *et al*. reported the use of triethylammonium formate as a hydrogen donor with the previously described ruthenium catalytic system.[47, 50]

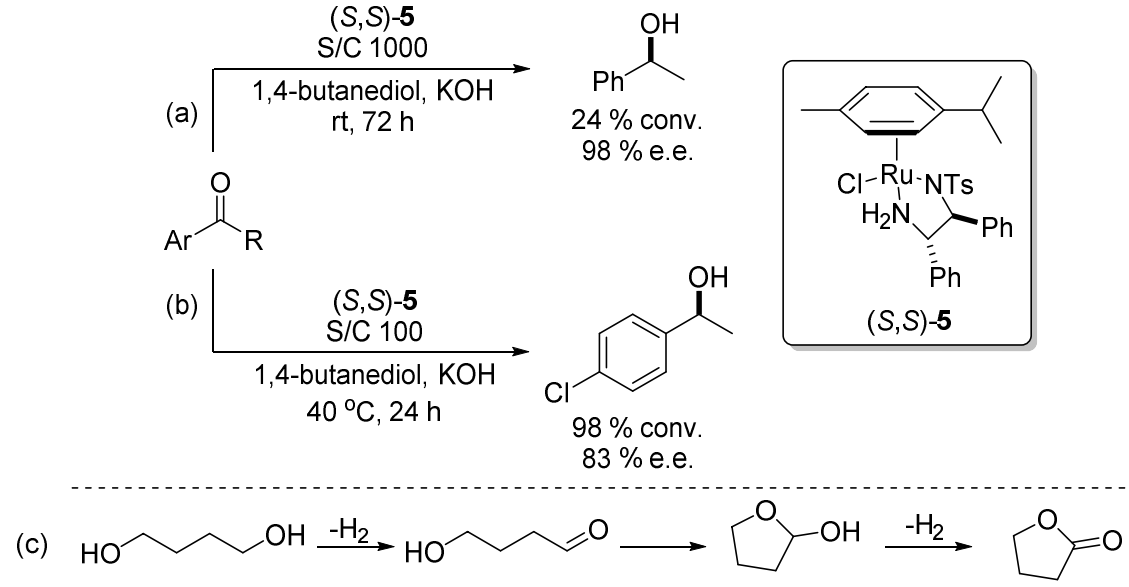


R	R'	Time	Yield %	e.e. % (config.)
H	Me	20	> 99	98 (*S*)
H	Et	60	96	97 (*S*)
m-Cl	Me	21	> 99	97 (*S*)
p-Cl	Me	24	> 99	95 (*S*)
p-CN	Me	14	> 99	90 (*S*)
m-OMe	Me	50	> 99	98 (*S*)
p-OMe	Me	60	> 99	97 (*S*)

Table 2 Asymmetric transfer hydrogenation of prochiral aromatic ketones using triethylammonium formate as the hydrogen donor.

As shown in Table 2 excellent yields and enantioselectivities were achieved with Noyori's new catalyst system.[50]

More recently, Williams and coworkers reported that 1,4-butanediol could be used as an irreversible reducing agent, in stoichiometric amounts, in transfer hydrogenation reactions (a and b, Scheme 8).[52, 53]



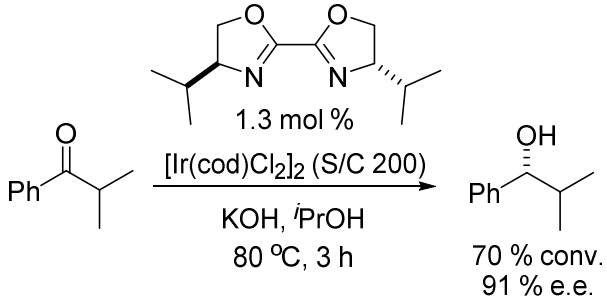
Scheme 8 Asymmetric transfer hydrogenation of prochiral aryl-alkyl ketones using 1,4-butanediol as the hydrogen donor.

Due to the irreversible formation of dihydrofuran-2(3*H*)-one (c, Scheme 8), 1,4-butanediol could be used in stoichiometric amounts instead of the large excess required with 2-propanol.[53] The asymmetric reduction of acetophenone gives the corresponding alcohol in an excellent 98 % e.e. however in a low 24 % conversion (a, Scheme 8). The conversion can be improved by increasing the catalyst loading (S/C) from 1000 to 100 however the enantioselectivity was much lower (83 % e.e.) for the reduction of 3-chloroacetophenone (b, Scheme 8).[53] Due to the relative inferiority of 1,4-butanediol as a hydrogen donor compared with 2-propanol it has not been extensively studied.

In addition to the advances made with ruthenium(II) catalysts for the asymmetric transfer hydrogenation of prochiral ketones, there have been several reports using both iridium(III)[54, 55] and rhodium(III)[56] complexes.

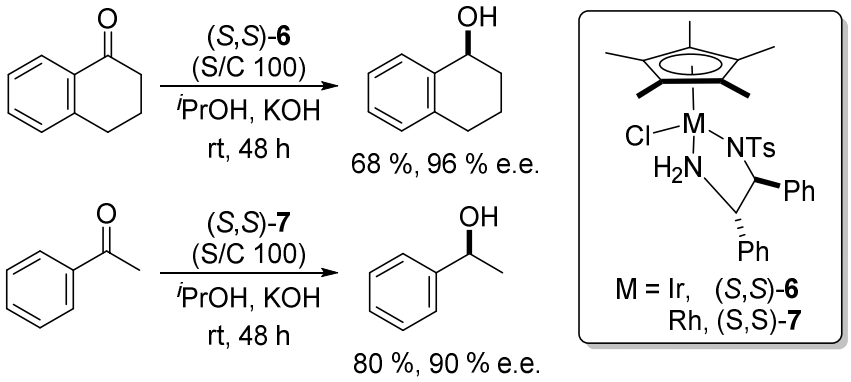
1.1.4 Ir(III) and Rh(III) Catalysed Asymmetric Transfer Hydrogenations of Prochiral Ketones.

In 1991, Pfaltz and coworkers showed that prochiral ketones could be reduced with a high degree of enantiofacial control using iridium(III) complexes (Scheme 9).[54, 57]



Scheme 9 First report of iridium catalysed asymmetric transfer hydrogenation of prochiral ketones.

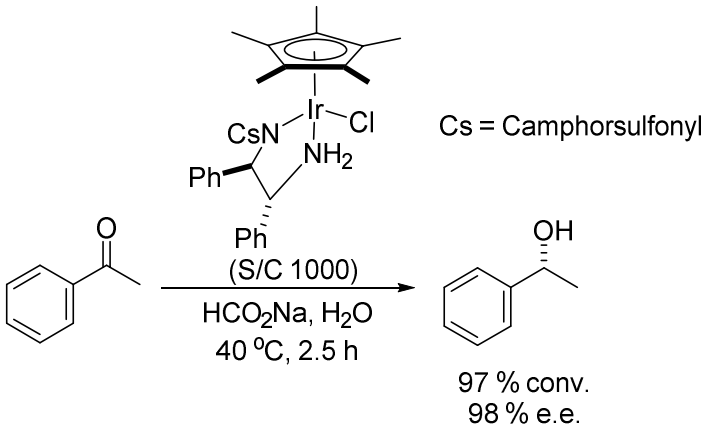
Shortly after it was shown that (*S*,*S*)-**6** and the analogous rhodium(III)[58] complex (*S*,*S*)-**7** with amino sulfonamide ligands were effective catalytic systems for the asymmetric transfer hydrogenation of aryl ketones (Scheme 10).[59, 60]



Scheme 10 Asymmetric transfer hydrogenation of aryl ketones with Ir(III) and Rh(III) catalysts.

Furthermore, Blacker and coworkers showed that (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol, (1*R*,2*S*)-(-)-norephedrine and other related amino-alcohol ligands could be used with the same iridium and rhodium dimers for the reduction of aryl ketones in high enantiomeric excess.[61]

In addition to the many reported examples of successful asymmetric transfer hydrogenations of prochiral ketones with 2-propanol and triethylammonium formate using iridium and rhodium catalysts,[62-69] there have been several reports of water-soluble versions using sodium formate as the hydrogen donor (Scheme 11).[70-72]



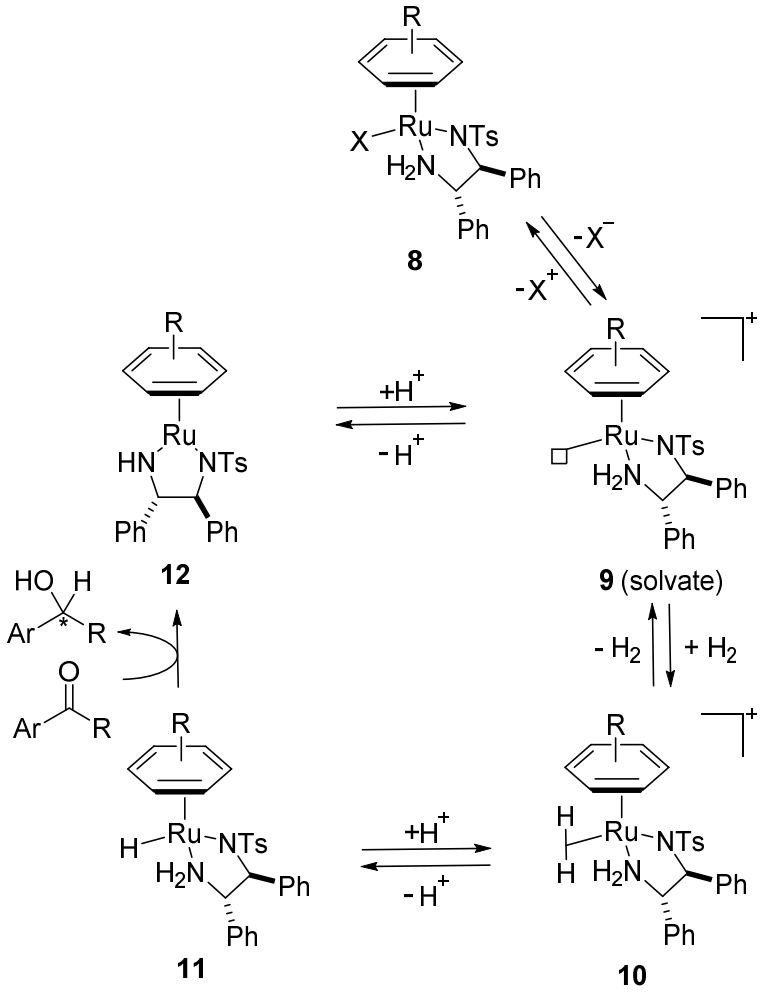
Scheme 11 Ir(III) catalyst for the ATH of acetophenone in water.

In spite of these major advances the use of ruthenium(II) complexes are more frequently used in asymmetric transfer hydrogenation reactions. More recently iridium(III),[73-75] rhodium(III)[76] and ruthenium(II)[77, 78] complexes have also been shown to be excellent

catalytic systems for asymmetric pressure hydrogenations of ketones (see **1.1.5** for ruthenium(II) catalysts).

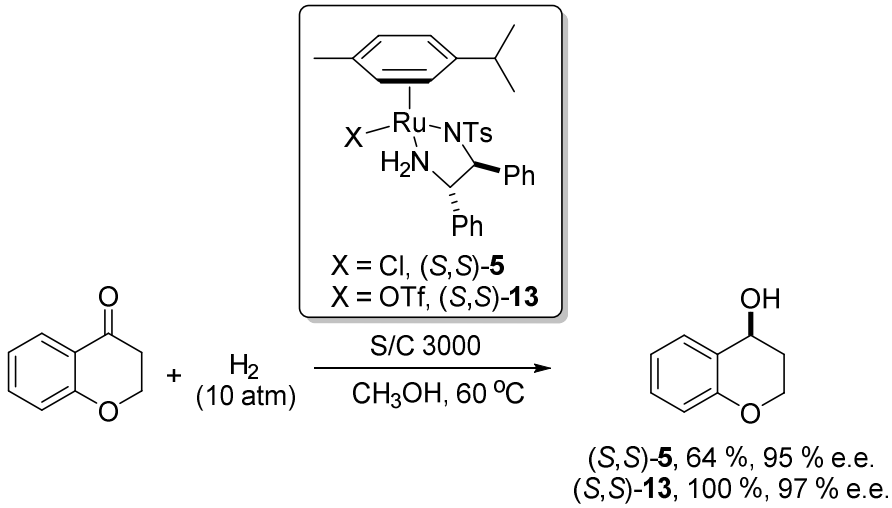
1.1.5 Ru(II) Catalysts for the Asymmetric Hydrogenation of Unfunctionalised Prochiral Ketones using Molecular Hydrogen.

Until 2006, most of the ruthenium-arene transfer hydrogenation catalysts in the literature were not compatible in asymmetric hydrogenations with molecular hydrogen.[77] Since the discovery that triflate analogues were better suited to pressure hydrogenation conditions compared to the corresponding chloride versions there have been several reports of the asymmetric reduction of prochiral ketones with molecular hydrogen using these catalysts.[77-81] The proposed mechanism is shown in Scheme 12.



Scheme 12 Catalytic cycle for the asymmetric hydrogenation of ketones with H_2.

In accordance with this proposed mechanism dissociation of the Ru-X species in the reaction solvent is essential before the cationic 16 electron ruthenium species can accept molecular hydrogen to form a η^2-H_2 complex. Deprotonation of **10** leads to the formation of the 18 electron Ru-H reductive species **11**.[77, 82, 83] When X = Cl the Ru-X bond is not fully dissociated in the required alcohol solvents.[77] Noyori and coworkers developed the ruthenium triflate analogue, which overcame this problem and lead the reduction of 4-chromanone in high yield and excellent enantiomeric excess at low catalyst loading (Scheme 13).[77]

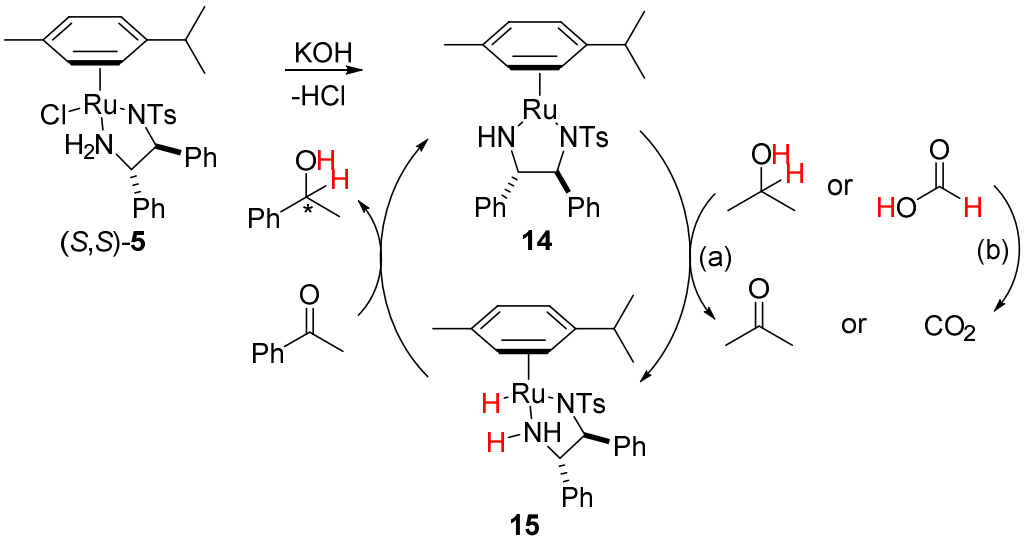


Scheme 13 Asymmetric pressure hydrogenation of 4-chromanone with Cl or OTf derivative of Ru(II) catalyst.

Following the success of this catalytic system[77, 78] Wills[79] and Ikariya[80, 81] reported the use of ruthenium 'tethered' catalysts for asymmetric pressure hydrogenation. Other systems have been developed for this transformation, such as iridium(III) and rhodium(III)-based catalysts.[73, 84] Despite these enormous advances in the field of asymmetric pressure hydrogenation, the previously discussed hydrogen donors such as 2-propanol and triethylammonium formate remove the requirement for molecular hydrogen, which renders the reaction safer and easier to perform.[85] Section **1.1.6** discusses the reported work towards elucidating the mechanism for asymmetric transfer hydrogenation reactions.

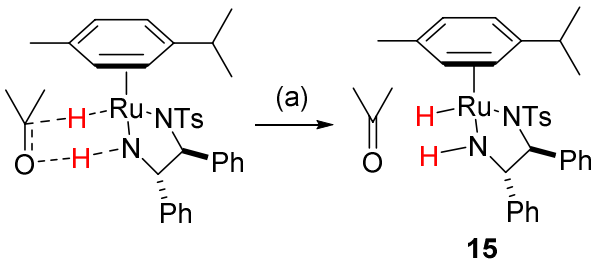
1.1.6 Mechanism for the Asymmetric Transfer Hydrogenation of Ketones.

In 1997, Noyori *et al*. reported the isolation of the catalyst precursor, the true catalyst and the reactive catalytic intermediate, which meant that the mechanism for this reaction is now well understood.[86] The reaction of [Ru(η^6-*p*-cymene)Cl_2]$_2$, (*S*,*S*)-TsDPEN and potassium hydroxide in an equimolar ratio in dichloromethane at room temperature lead to the formation of the catalyst precursor (*S*,*S*)-**5** as orange crystals.[86] The reaction of the catalyst precursor with one equivalent of potassium hydroxide in dichloromethane and water gave the true catalyst **14** as deep purple crystals.[86] The reactive catalyst **15** was isolated as yellow needles after the treatment of the deep purple complex with 2-propanol and subsequent recrystallisation.[86] The conformation of these structures by X-ray crystallography led to the proposal of the catalytic cycle shown in Scheme 14.



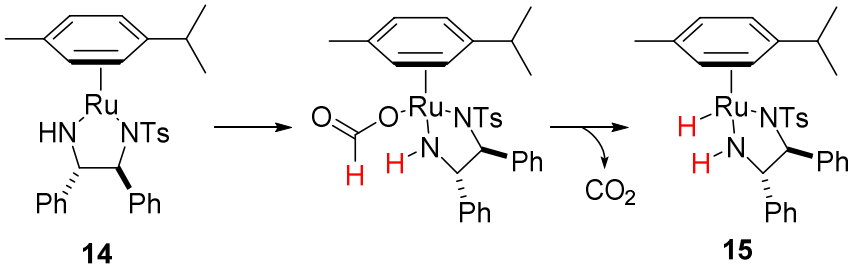
Scheme 14 Mechanism for the asymmetric transfer hydrogenation of prochiral ketones.

The addition of strong base leads to the facile elimination of HCl to give the 16-electron true catalytic species **14** (Scheme 14). The oxidation of 2-propanol to acetone allows the conversion of this species to the 18-electron reactive intermediate **15**. One of the hydrogens from 2-propanol is transferred to the ruthenium and the other is transferred to the unprotected nitrogen (Scheme 15).



Scheme 15 Oxidation of 2-propanol to form the 18-electron reactive intermediate **15**.

When triethylammonium formate is used the formate is thought to bond to the metal through an oxygen atom and subsequent loss of CO_2 leads to the formation of the 18-electron reactive intermediate **15** (Scheme 16).



Scheme 16 Formation of the 18-electron reactive intermediate *via* loss of CO_2.

The prochiral ketone can then be reduced by the 18-electron reactive intermediate **15** to give its corresponding enantiopure alcohol, in this case acetophenone to (*S*)-1-phenylethanol. During this step the hydridic Ru-H and protic N-H in the 18-electron reactive intermediate **15** are transferred to the carbonyl carbon and carbonyl oxygen respectively.

The stereodetermining step in the catalytic cycle is generally imposed by a directing functional group that interacts with the complex. Aryl groups such as phenyl,[50] bicyclics[50] and heteroatom-containing aromatics[87] are amongst the most common directing groups for this transformation. DFT calculations performed by Noyori *et al.* suggested that the CH/π attractive interaction between the η^6-arene ring and the aryl substituent in the prochiral ketone could stabilise the transition state and hence lead to the high enantioselectivities of the products.[88]

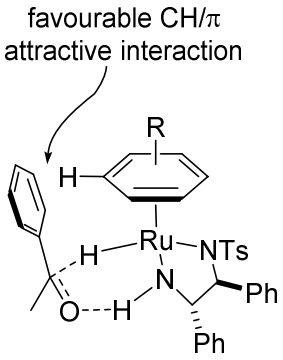
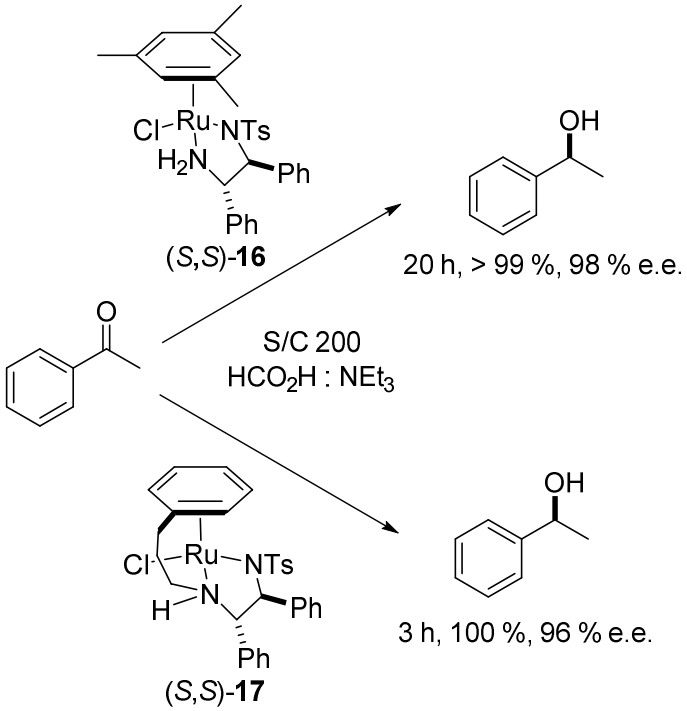


Figure 8 Favourable CH/π attractive interaction in the diastereomeric transition state for aryl-alkyl reductions.

Following Noyori's recent development in asymmetric transfer hydrogenation catalysis[47, 50, 89, 90] further ruthenium(II) catalytic systems were developed.[87, 91-95]

Amongst the most reactive systems was the 'reverse-tethered' catalyst (*S*,S)-**17** reported by Wills and coworkers (Scheme 17).



Scheme 17 Comparison of (*S*,*S*)-**16** and (*S*,*S*)-**17** for the reduction of acetophenone.

Wills *et al*. went on to show that various aryl-containing prochiral ketones can be reduced in excellent yields and enantiomeric excesses (Figure 9) with far superior reactivity than previously reported systems.[87]

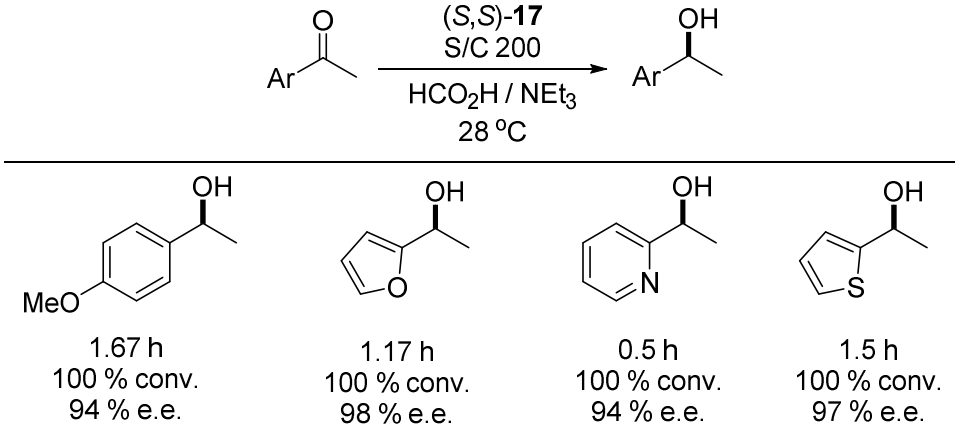


Figure 9 Asymmetric transfer hydrogenation of aryl-alkyl ketones using 'reverse-tethered' (*S*,*S*)-**17**.

Figure 10 shows the proposed CH/π attractive interactions for the asymmetric transfer hydrogenation of aryl-alkyl ketones using Wills' 'reverse-tethered' (*S*,*S*)-**17**.

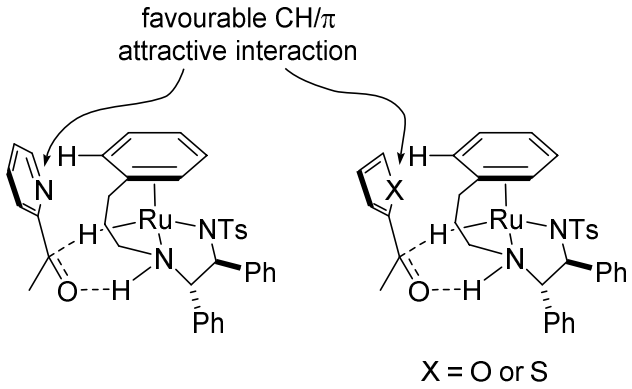


Figure 10 Favourable CH/π attractive interaction in the diastereomeric transition state for the reduction of aryl-alkyl ketones with (*S*,*S*)-**17**.

Since the extensive reports of asymmetric transfer hydrogenations of aryl-alkyl ketones there have been discoveries of other directing groups for this transformation (**1.1.7**).

1.1.7 Other Directing Groups for Asymmetric Transfer Hydrogenation.

In 1997, Noyori *et al*. discovered that propargylic ketones could be reduced in excellent yields and enantioselectivities with asymmetric transfer hydrogenation.[96] The stereoselective addition of the hydride is attributed to a CH/π attractive interaction (Figure 11), similar to that previously reported for aryl-alkyl prochiral ketones (Figure 8 and Figure 10).[96]

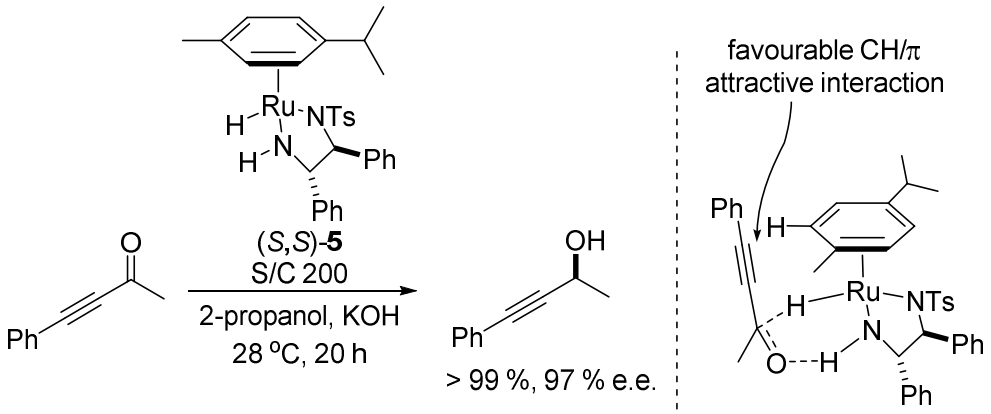


Figure 11 Asymmetric reduction of a propargylic ketone in high enantiomeric excess and the proposed CH/π attractive interaction.

Since the introduction of the alkyne moiety as a powerful directing group for asymmetric transfer hydrogenation there has been several reports using this chemistry for the synthesis of key intermediates of natural products and medicinally relevant compounds.[97-118]

In a similar manner to both aryl-alkyl and alkyne-alkyl prochiral ketones, the olefin functionality has been shown to direct the stereospecificity of the hydride transfer. The asymmetric reduction of cyclic α,β-unsaturated ketones consistently give better selectivities than acyclic versions.[119, 120] This is attributed to a geometric restraint of cyclic enones (Figure 12) meaning that they are not able to form the s-*cis* configuration required for 1,4-hydride addition and as a result give only the 1,2-reduction product (Figure 12).[119]

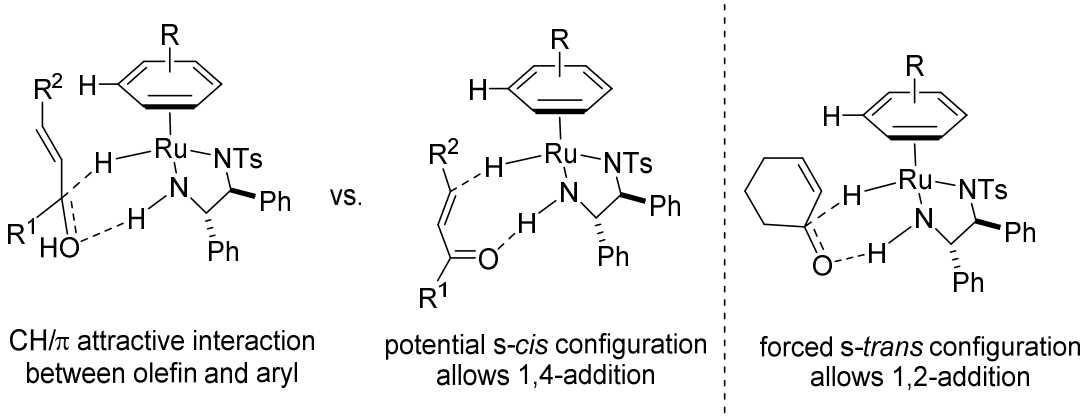
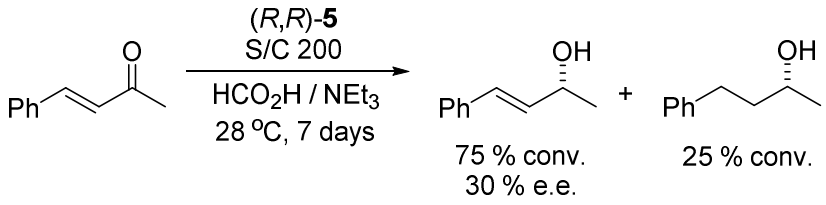


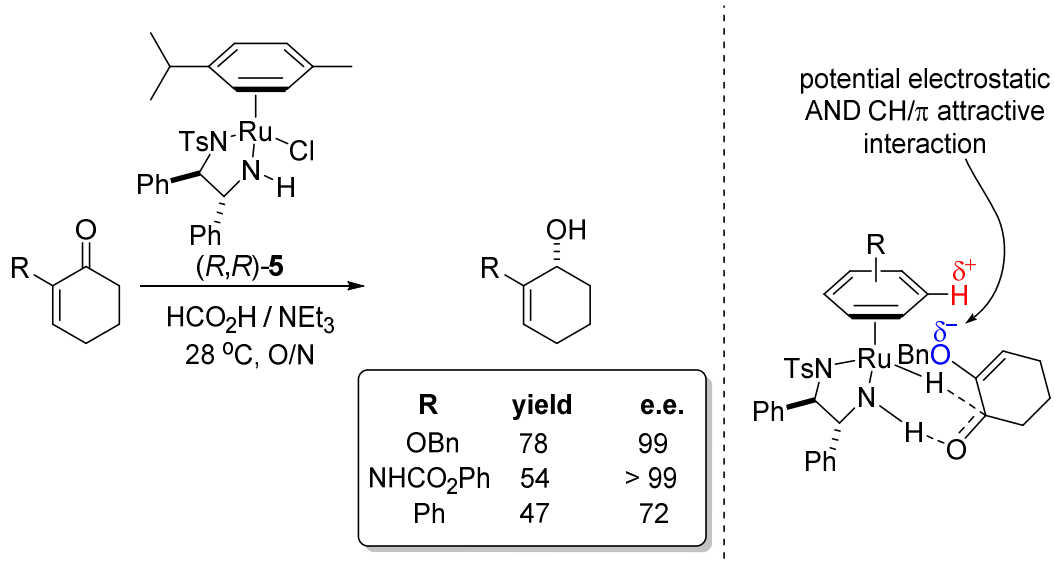
Figure 12 Diastereomeric transition states of cyclic and acyclic α,β-unsaturated ketones.

Since acyclic enones have a less rigid structure they are able to form the s-*cis* configuration as well as the s-*trans* configuration.[119] The asymmetric reduction of benzylideneacetone gives a mixture of saturated and unsaturated products (Scheme 18). The allylic alcohol is formed in the (*R*)-configuration, which supports the suggestion that a CH/π interaction exists between the olefin and the η^6 arene ring, despite only giving the product in 30 % e.e (Scheme 18).[119]



Scheme 18 Asymmetric transfer hydrogenation of benzylideneacetone with (*S*,*S*)-**5**.

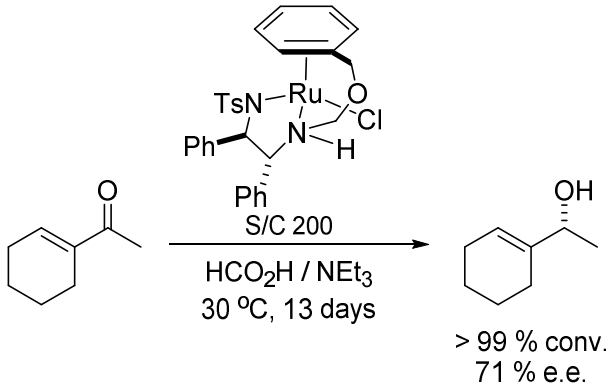
The asymmetric reduction of cyclic α,β-unsaturated ketones (Figure 13) gives only the unsaturated product as a result of 1,2-hydride addition.[119] When R is OBn or $NHCO_2Ph$ the products were achieved in excellent enantiomeric excess. This could be due to a combination of CH/π attractive and electrostatic interactions (see Figure 13 for R = OBn reduction TS). The enantioselectivity when R is phenyl was significantly lower at 72 %, which could be due to the unfavoured orientation of the phenyl ring.



R	yield	e.e.
OBn	78	99
$NHCO_2Ph$	54	> 99
Ph	47	72

Figure 13 Asymmetric transfer hydrogenation of cyclic α,β-unsaturated ketones to give their corresponding enantiomerically enriched allylic alcohols.

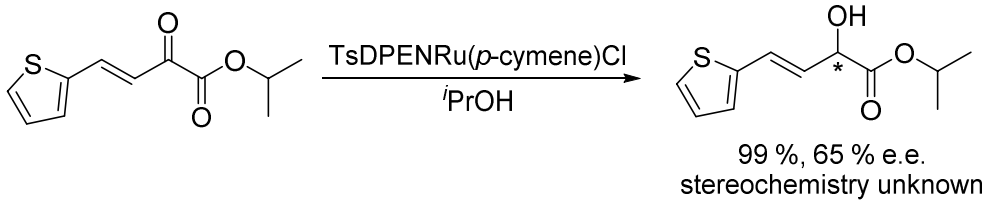
Furthermore, if the alkene moiety is present in a ring then only the unsaturated allylic alcohol will be furnished. This is shown by the asymmetric transfer hydrogenation of 1-acetyl-1-cyclohexene which gives only the (*R*)-1-cyclohexene-1-methanol in a moderate 71 % e.e (Scheme 19).[120] It has been shown that the more rigid cyclic enones react with greater enantiofacial control.[120]



Scheme 19 Asymmetric transfer hydrogenation of and α,β-unsaturated ketone.

In the literature there are other examples for the asymmetric transfer hydrogenation of α,β-unsaturated ketones that show comparable results to those above.[121] Furthermore, iridium catalysed transfer hydrogenation has been used for the reduction of both cyclic and acyclic enones, although these are generally not as successful as their ruthenium analogues.[122-127]

Interestingly, the reduction of an β,γ-unsaturated-α-ketoester using 2-propanol as the hydrogen donor proceeds in excellent yield and a moderate 65 % e.e. (Scheme 20).[128]



Scheme 20 Asymmetric transfer hydrogenation of β,γ-unsaturated-α-ketoester.

This suggests that the stereoselective hydride transfer is directed by either the alkene[119-121] or ester[129-131] moiety. Since the absolute configuration of the product is unknown it is not possible to identify which is the directing group in this case (Scheme 20).[128]

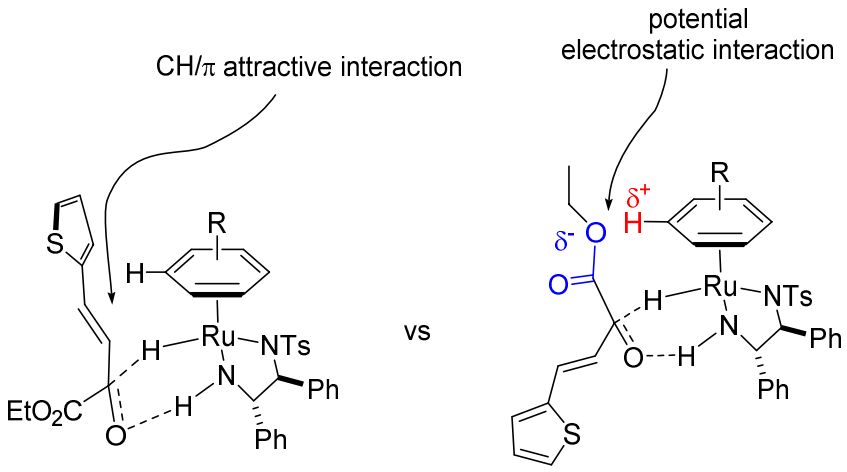
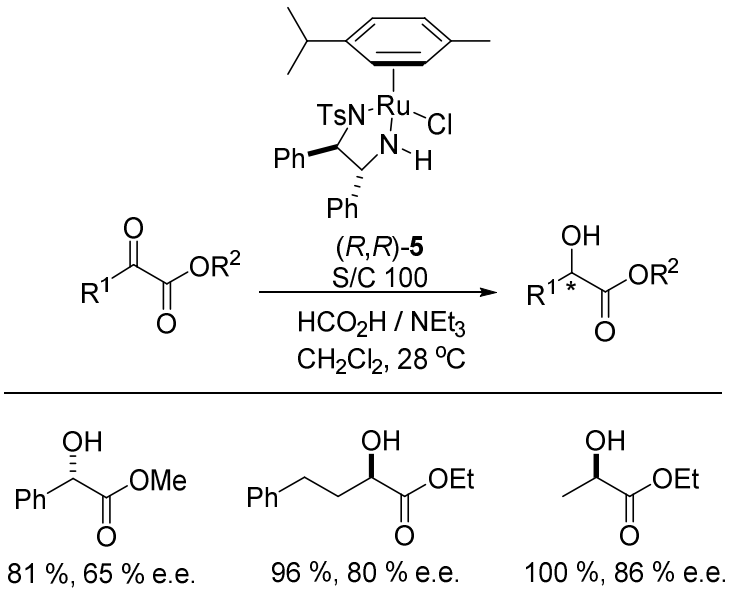


Figure 14 Competing directing groups in the diastereomeric transition state: alkene vs ester.

The ester moiety has been previously shown as a directing group for transfer hydrogenation, and this is highlighted in Scheme 21.[130]

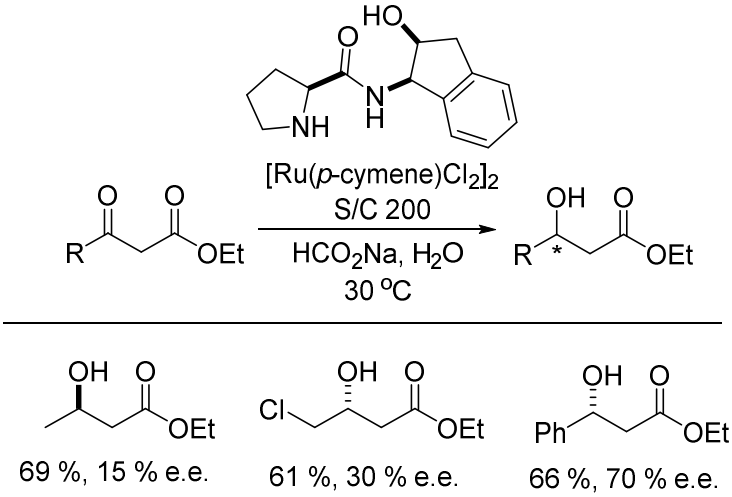


Scheme 21 The ester moiety as a directing group for asymmetric transfer hydrogenation.

When R^1 is phenyl the enantiomeric excess deteriorates with respect to acetophenone[50] however the product remains in the (*S*)-configuration. This suggests the phenyl moiety remains as the directing group for this transformation despite some competition of the ester functionality. When the phenyl is replaced by phenethyl the enantiomeric excess is increased to 80 % but the product is now in the (*R*)-configuration.[130] This implies that

since the phenyl group is too distant the ester moiety is interacting with the η^6-arene, potentially through an electrostatic interaction (Figure 14). Additionally when the phenyl moiety is removed altogether and replaced with a methyl group the enantiomeric excess still remains high at 86 % and in the (*R*)-configuration, supporting the existence of the electrostatic interaction.[130] These results suggest that although the ester moiety is able to direct hydride transfer it is not as powerful as phenyl.

When the ester moiety is one carbon further away it can still act as a directing group even though to a much lesser extent as shown by the reduction of ethyl acetoacetate to give the corresponding alcohol in 15 % enantiomeric excess (Scheme 22).[131] Furthermore, it was shown that ethyl 4-chloroacetoacetate is reduced with the opposite sense of induction as ethyl acetoacetate indicating that the α-chlorine atom in this case is a more powerful directing group than the distant ester moiety (Scheme 22).[131]



Scheme 22 Directing group comparison between β-ester moiety and α-chlorine atom.

Ethyl 4-chloroacetoacetate is reduced with the same sense of induction as ethyl benzoylacetate however to a much lesser extent.[131] The proposed electrostatic interaction between the chlorine atom and the η^6-arene ring is shown in Figure 15.

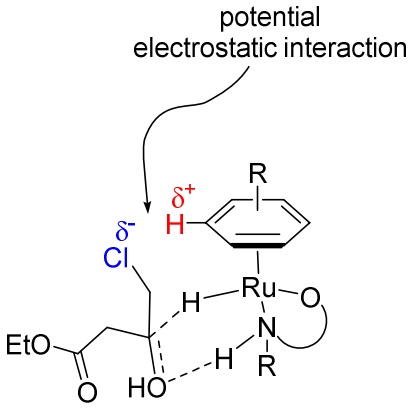


Figure 15 α-Chlorine atom as a directing group for asymmetric transfer hydrogenation.

The oxygen from ether linkages has also been shown to direct the hydride addition.[132-135] The asymmetric reduction of phenoxy-2-propanone gives the corresponding alcohol in 29 % e.e (major enantiomer unknown, Figure 16).[132] This indicates that the oxygen atom might impose some sense of induction (Figure 16), even if only marginally.

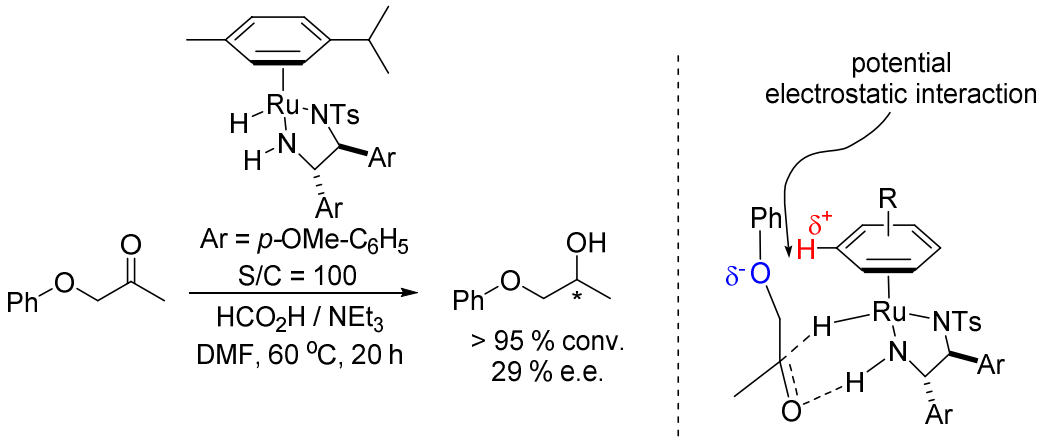
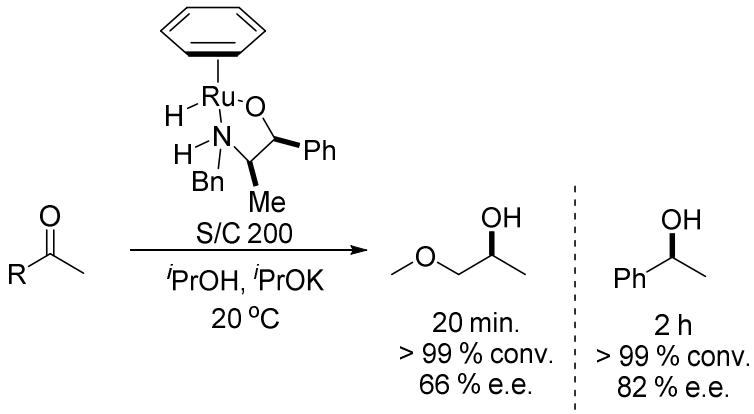


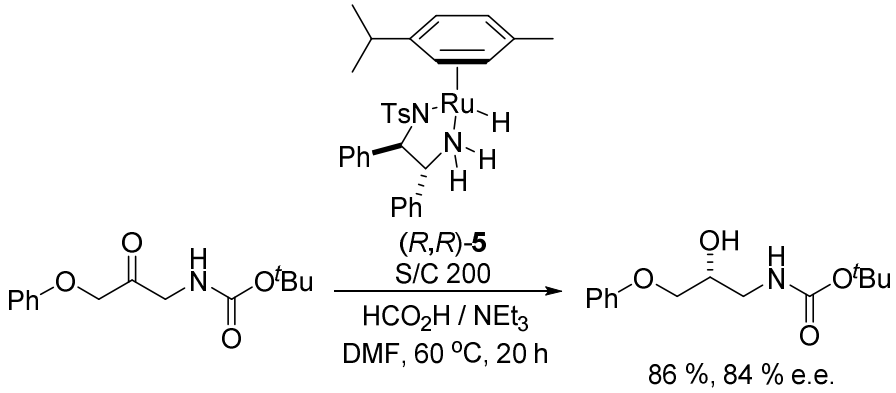
Figure 16 Oxygen atom as a directing group for asymmetric transfer hydrogenation.

Carpentier *et al*. showed that the reduction of methoxyacetone gave the (*S*)-alcohol in excellent conversion (> 99 %) and a moderate 66 % e.e. after only 20 minutes.[133] This was reduced with the same sense of induction as acetophenone (Scheme 23), supporting the existence of the proposed electrostatic interaction.[133]



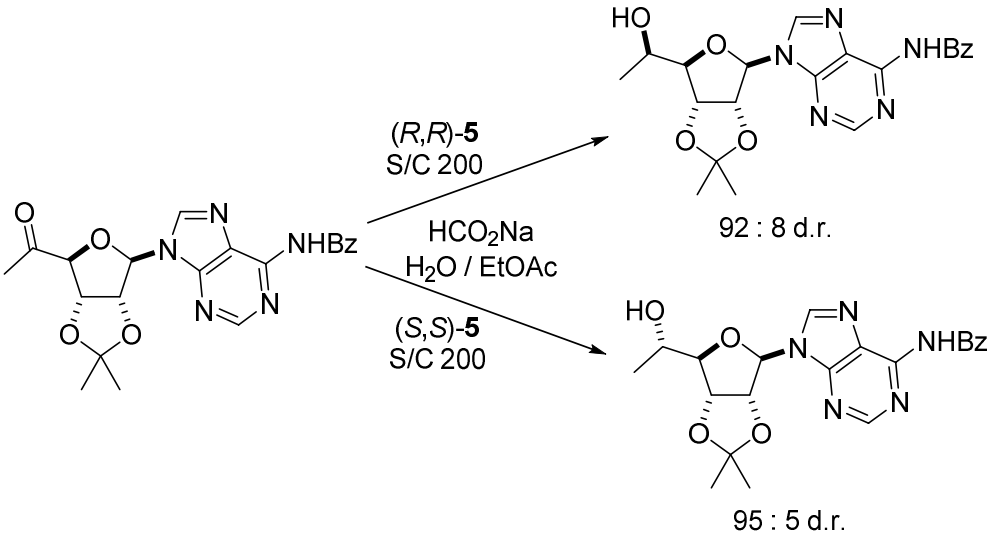
Scheme 23 Comparison of the asymmetric transfer hydrogenation of methoxyacetone with acetophenone.

Wills and coworkers also showed that an α-phenoxyketone could be reduced using the triethylammonium formate transfer hydrogenation conditions to give the corresponding (*R*)-alcohol in a good 84 % e.e. (Scheme 24).



Scheme 24 Phenoxy moiety as a directing group in an asymmetric transfer hydrogenation reaction.

More recently, Bligh and coworkers reported a tetrahydrofuran-directed transfer hydrogenation in aqueous sodium formate.[135] The THF-bearing ketone is reduced with complete catalyst control to give the corresponding alcohol product in excellent diastereomeric excess (Scheme 25).



Scheme 25 ATH of with complete catalyst control.

The authors proposed that the high enantiofacial control was enforced by a stabilising CH/'high electron density' interaction.[135] It is possible that the high degree of stereoselectivity could be induced further by the heterocycle, however the extent at which it contributes cannot be determined from this experiment.

Aside from CH/π and 'high electron density' interactions, alkyl-alkyl ketones have been shown to reduce with good enantioselectivity with transfer hydrogenation catalysts. Wills *et al*. showed that 1-cyclohexylethan-1-one could be reduced with high enantioselectivity using a hindered 'reverse-tethered' version of their catalyst (*S*,*S*)-**18** (Figure 17). To date this is the best result for the reduction of alkyl-alkyl ketones using TsDPEN catalysts.[89, 92]

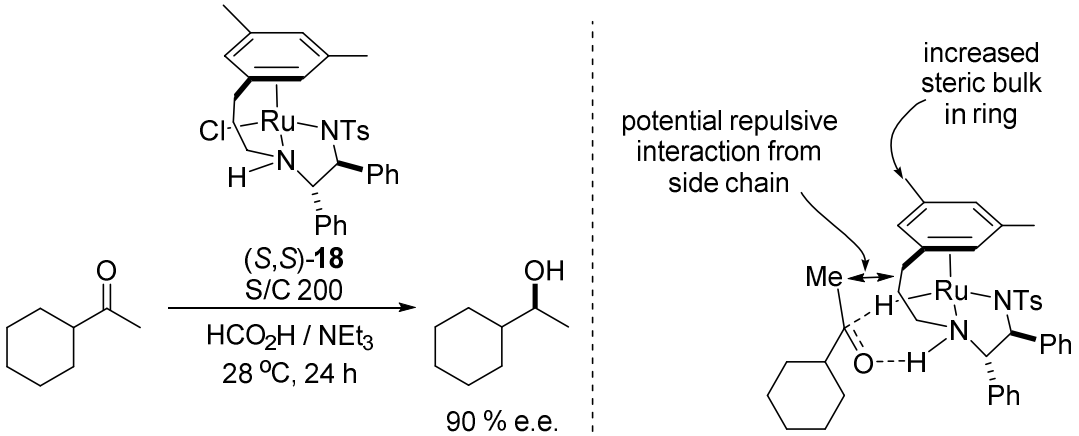
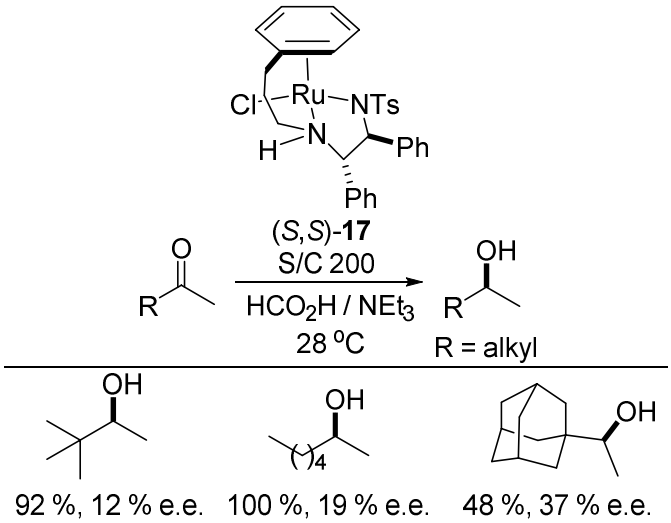


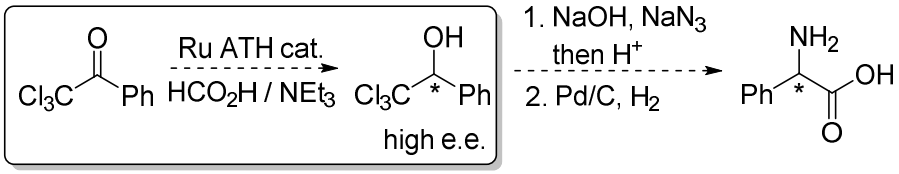
Figure 17 ATH of cyclohexyl methyl ketone with (*S*,*S*)-**18**.

The high degree of enantiocontrol was thought to be because of a potential repulsive interaction with one of the substituents and the side chain (Figure 17).[87] Since other alkyl-alkyl ketones were reduced with some degree of enantioselectivity this explanation seemed likely (Scheme 26).[87]



Scheme 26 ATH of alkyl-alkyl ketones using (*S*,*S*)-**17**.

Following the vast amount of research into directing groups for asymmetric transfer hydrogenation, we wanted to investigate the trend in reduction of α-chlorinated acetophenone derivatives. It was the aim of my Masters project in the Fox group to synthesise enantiomerically enriched 2,2,2-trichloro-1-phenylethan-1-ol for its use in a Corey-Link reaction (Scheme 27).[136, 137]



Scheme 27 Proposed route for the synthesis of enantiomerically enriched aryl trichlorocarbinols.

The only α-chlorinated acetophenone that has been previously reduced with asymmetric transfer hydrogenation was 2-chloroacetophenone.[87, 93, 138, 139] Therefore we chose to investigate how the successive addition of chlorine at the α-position of acetophenone

affected the conversions, yields and enantioselectivities of their transfer hydrogenation reactions (**1.1.8**).[140]

1.1.8 Asymmetric Transfer Hydrogenation of α-Chlorinated Acetophenones.

It was reported in the literature that the asymmetric reduction of 2-chloroacetophenone was particularly challenging for ruthenium-based transfer hydrogenation catalysts in 2-propanol.[87] Some of the best results for this transformation were completed with rhodium(III) and 'reverse-tethered' ruthenium(II) catalysts in triethylammonium formate.[87, 93, 138, 139]

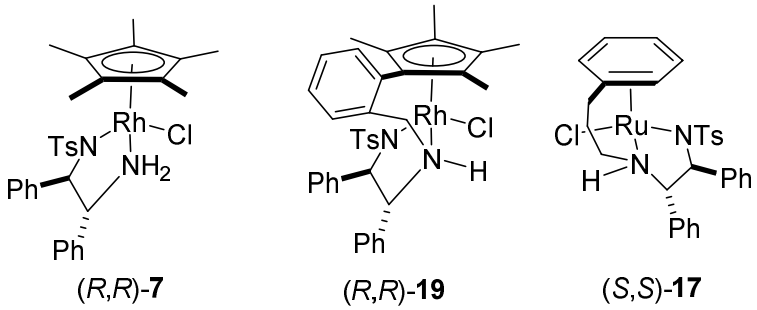
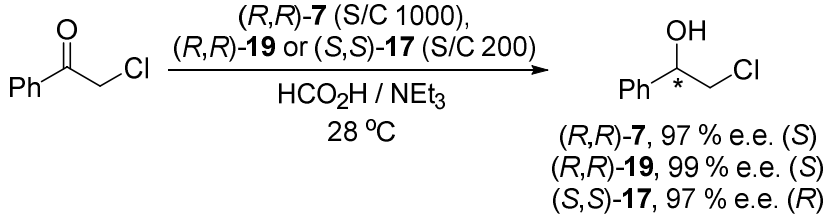


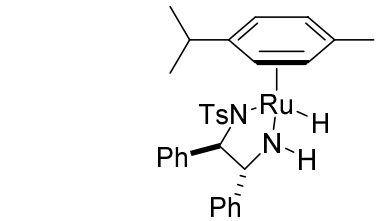
Figure 18 Most successful catalysts for the ATH of α-chloroacetophenone.

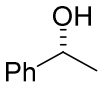
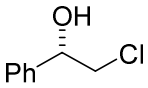
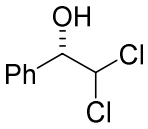
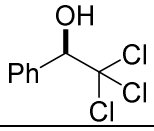
The asymmetric transfer hydrogenation of α-chloroacetophenone using the catalysts in Figure 18 are reported in the literature (Scheme 28) and each give 2-chloro-1-phenylethan-1-ol in excellent enantiomeric excess.[93, 139, 141]



Scheme 28 ATH of 2-chloroacetohphenone with Ru(II) and Rh(III) transfer hydrogenation catalysts.

With this in mind we investigated the ruthenium(II) catalysed asymmetric transfer hydrogenation of α-chlorinated acetophenones, with (*R*,*R*)-**5**, using triethylammonium formate as the hydrogen donor (Table 3).[142]



R	Yield %	e.e.[a] %	Product	Structure
CH_3	95	95	(*R*)[b]-**20**	
CH_2Cl	77	96	(*S*)[b]-**21**	
$CHCl_2$	69	64	(*S*)[b]-**22**	
CCl_3	83	27	(*R*)[b]-**23**	

[a] by HPLC analysis. [b] from sign of rotation.

Table 3 Asymmetric transfer hydrogenations of α-chlorinated ketones with (*R,R*)-**5** and triethylammonium formate.

The results indicate that while 2,2-dichloroacetophenone is reduced with the same sense of asymmetric induction as acetophenone and 2-chloroacetophenone, the major enantiomer of the trichloro-product (*R*)-**23** results from the opposite facial attack, albeit with lower enantiomeric excess (Table 3).[140] The stereochemistry of the 2,2,2-trichloroacetophenone reduction suggests that the trichloromethyl group is a more powerful directing group in an asymmetric transfer hydrogenation reaction than phenyl, reversing the traditional sense of asymmetric induction for acetophenone and related compounds.[143] From these results it was suggested that the trichloromethyl group was directing the stereoselective hydride addition (Figure 19).

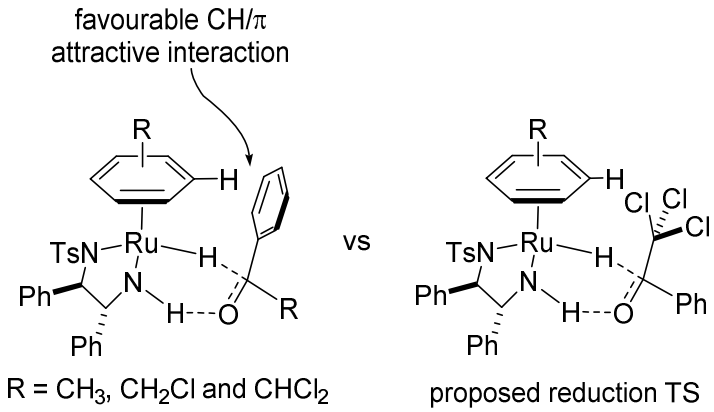
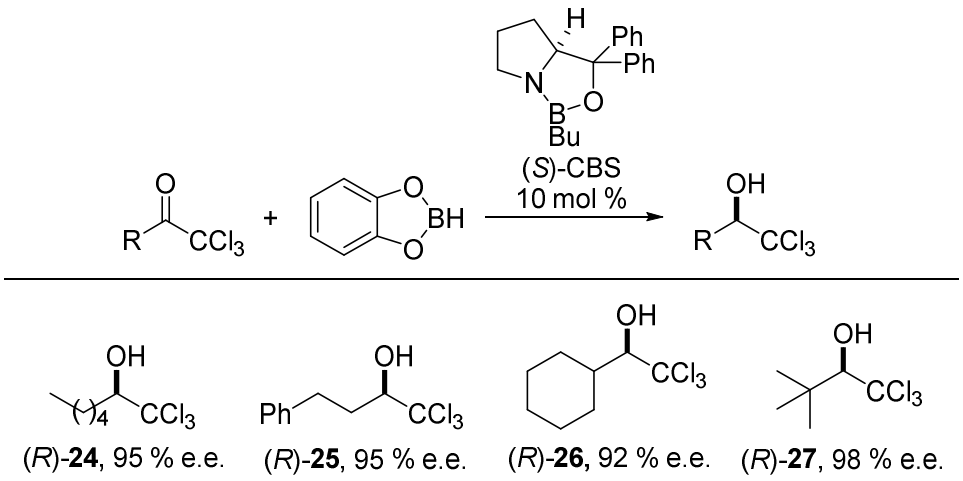


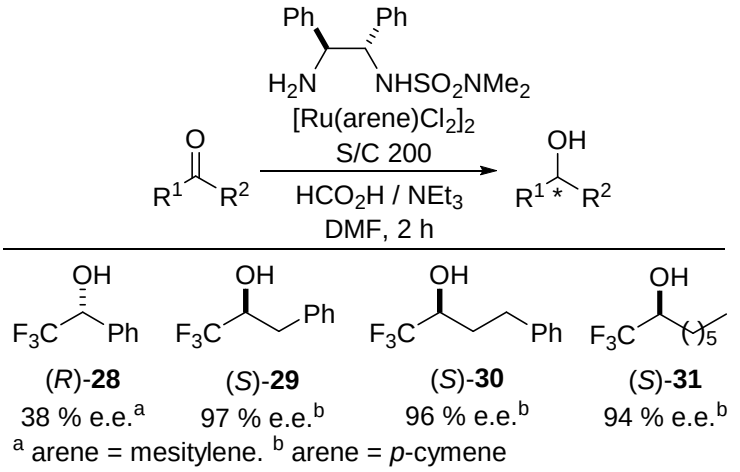
Figure 19 Favourable CH/π attractive interaction vs proposed electrostatic interaction.

The trichloromethyl group has previously been shown to direct the hydrogenation for the CBS-reduction ((*R*)-**24**-**27**, Scheme 29).[136, 137, 144, 145] The extent at which the trichloromethyl group controls the stereoselectivity is not fully understood.[136]



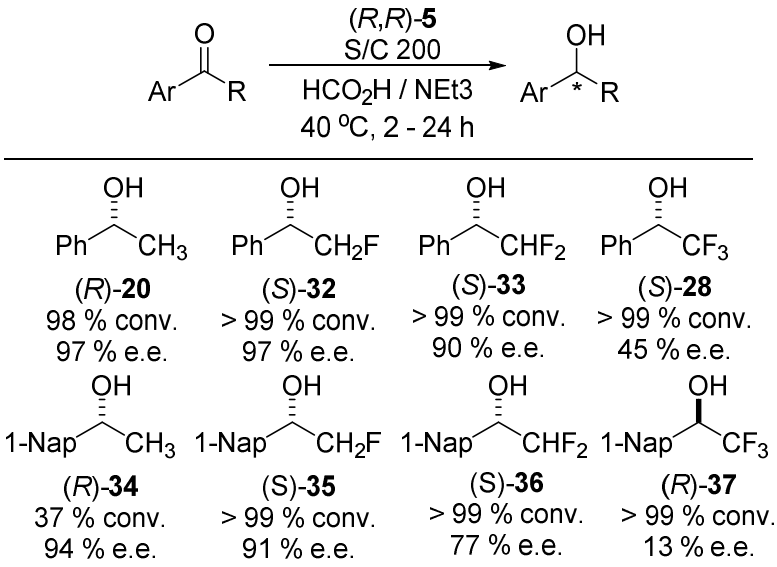
Scheme 29 CBS-reduction of trichloromethyl ketones.

It was at this point when we noticed in the literature that the trifluoromethyl group could similarly direct the stereoselective hydride addition in the transfer hydrogenation of alkyl/trifluoromethyl ketones.[129, 146, 147] Mohar *et al*. noticed that 1,1,1-trifluoro-3-phenyl-2-propanone was reduced with the opposite sense of asymmetric induction to give (*R*)-**29** compared with that of acetophenone[129] and 2,2,2-trifluoroacetophenone (Scheme 30).[146]



Scheme 30 ATH of 2,2,2-trifluoroacetohphenone and trifluoromethyl-alkyl ketones.

The opposite sense of asymmetric induction for the reduction of alkyl-trifluoromethyl ketones ((*S*)-**29**-**31**) was attributed by Mohar *et al*. to the trifluoromethyl group being larger than a methylene group.[146] Since 2,2,2-trifluoroacetophenone was reduced with the same sense of induction as acetophenone the authors proposed that the relative order of magnitude of group bulkiness for this reaction is Ph > CF_3 > cyclohexyl > CH_2.[146] Furthermore, the series in Scheme 31 indicates that the trifluoromethyl group significantly reduces the enantiomeric excess with respect to the 2,2-difluoromethyl moiety and in fact the reduction of 1-napthyl trifluoroketone gave the corresponding alcohol (*R*)-**37** with the opposite stereochemistry.[147]



Scheme 31 Asymmetric transfer hydrogenation of α-fluorinated-aryl ketones.

The authors suggested that since the size of a phenyl and trifluoromethyl group are similar in size the lower enantiomeric excess for (*S*)-2,2,2-trifluoro-1-phenylethan-1-ol (*S*)-**28** (45 % e.e.) could be attributed to their minor size differences.[147] It was suggested that the 1-napthyl analogue led to less favourable CH/π interactions due to sterics reasons, i.e. 1-napthyl being larger than phenyl in non-planar ketones and arenes.[147] Since the reduction of 1-acetonapthone with the same catalytic system gives the expected configuration of alcohol **34** in an excellent 94 % e.e., albeit with lower conversion, it appears that subtle differences in the diastereomeric transition states can lead to the difference in selectivity. Additionally, it has been shown that the 1-napthyl moiety is an excellent directing group giving the corresponding alcohols in excellent conversions and enantiomeric excesses with several other ruthenium transfer hydrogenation catalysts.[47, 50, 94, 130, 148-155] With this in mind, it was suggested that the lower enantioselectivity of (*R*)-2,2,2-trifluoro-1-(naphthalen-1-yl)ethan-1-ol (*R*)-**37** is not related to the relative size of the 1-napthyl and trifluoromethyl group but rather to the increase in size of the trifluoromethyl group compared with that of a methyl group.[147] The diastereomeric reduction transition states suggested by the authors are shown in Scheme 31.[147]

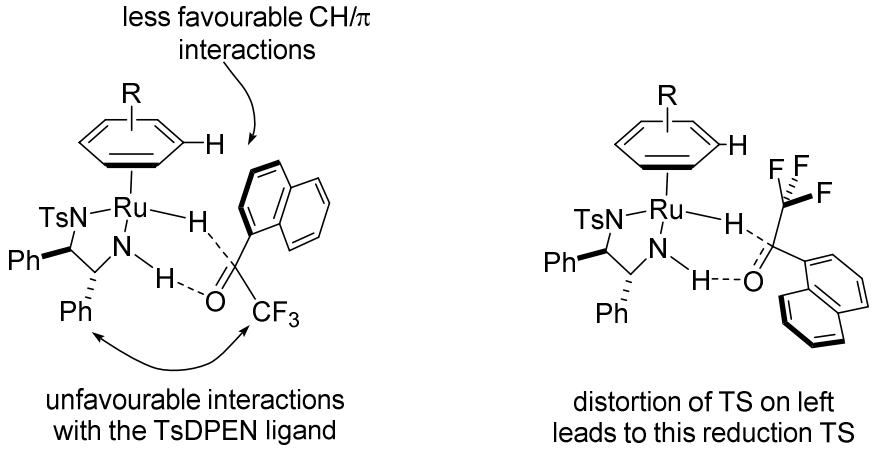


Figure 20 Diastereomeric reduction transition states for the reduction of trifluoromethyl ketones.

Aside from ruthenium(II) catalysed asymmetric transfer hydrogenation, pinene-derived boranes have been shown to reduce trifluoromethyl ketones with high enantiomeric excess with some interesting results. The reduction of 2,2,2-trifluoroacetophenone with (–)-β-diisopinocampheyl chloroborane ((–)-DIP-chloride) gives the (*S*)-enantiomer of product (*S*)-**28** (Figure 21), indicating that the trifluoromethyl group is in fact larger than phenyl,[143, 156] which is opposite to that suggested by Mohar[146] and Hoff.[147]

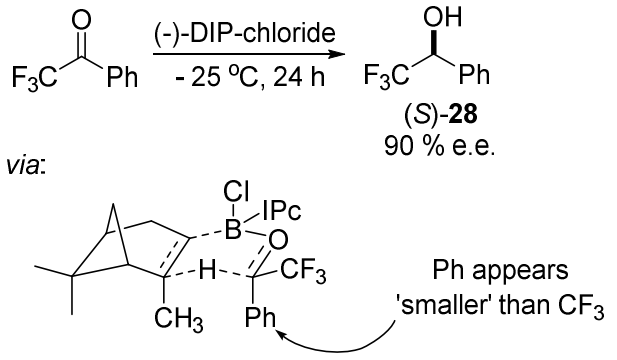


Figure 21 Reduction of 2,2,2-trifluoroacetophenone with (–)-DIP-chloride.

In 1993, Ramachandran *et al*. surveyed all the asymmetric reductions of 2,2,2-trifluoroacetophenone to date and compared the sense of induction with that of acetophenone.[156] They discovered that there was no obvious trend in the stereochemistry of 2,2,2-trifluoro-1-phenylethanol. Stereoselective reagents such as (*R*)-BINAL-H,[157, 158] lithium (1*S*,5*S*)-9-[(1*R*,2*R*,3*S*,5*R*)-2-[2-(benzyloxy)ethyl]-6,6-dimethylbicyclo[3.1.1]heptan-3-yl]-9-borabicyclo[3.3.1]nonan-9-uide (NB-Enantride),[159] potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K-Glucoride)[160] and β-isopinocampheyl-9-borabicyclo[3.3.1]nonane ((*R*)-Alpine-Borane)[161, 162] gave the expected major enantiomer of 2,2,2-trifluoro-1-phenylethanol, whilst Mosher's reagent,[163] (*S*)-CBS catalyst[164] and (–)-DIP-chloride reduced 2,2,2-trifluoro-1-phenylethan-1-one with the opposite sense of induction. Interestingly, mechanistically similar reductions with (*R*)-

Alpine-Borane[165] and (–)-DIP-chloride[166] gave opposite major enantiomers (Figure 21 and Figure 22).

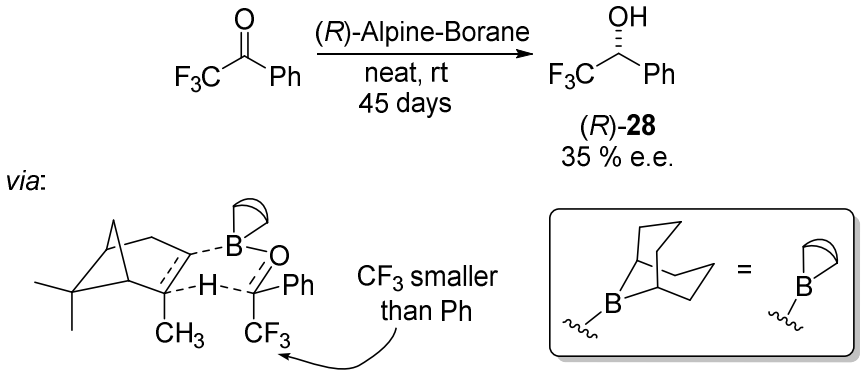


Figure 22 Reduction of 2,2,2-trifluoroacetophenone with Alpine-Borane.

Following these results Ramachandran and coworkers suggested that the enantio-directing trifluoromethyl group could be attributed to a combined steric and electronic influence of the fluorine atoms.[156]

More recently, Ramachandran and coworkers further investigated and compared the influence of fluorine and chorine in halo-ketones.[143] They showed that chlorine and fluorine behaved in the same way for their reductions. Whilst 2,2,2-trichloroacetophenone was reduced with the opposite sense of induction as acetophenone, 2-chloro- and 2,2-dichloroacetophenone were reduced with the same sense of induction as acetophenone with (–)-DIP-chloride (Figure 23).[143]

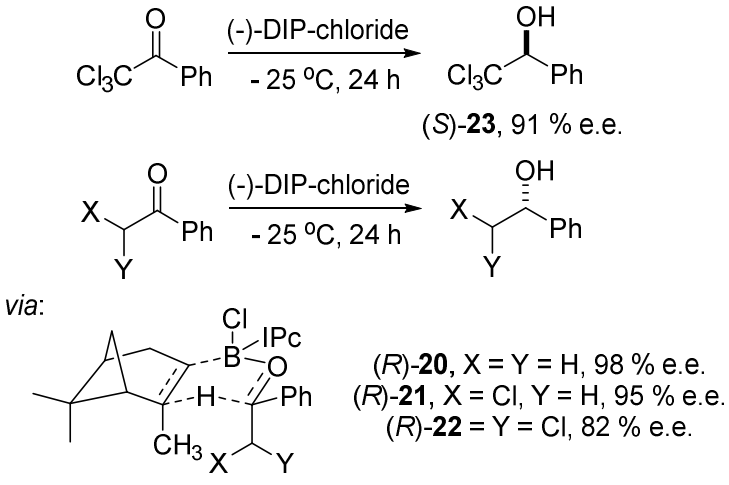


Figure 23 Reduction of chlorinated acetophenones with (–)-DIP-chloride.

Reduction of 2,2,2-trichloroacetophenone with (*R*)-Alpine-Borane gives the (*R*)-enantiomer of product opposite to that with (–)-DIP-chloride, which was also the case with 2,2,2-trifluoroacetophenone.[143] In order to understand the influence of the trihalo group Ramachandran *et al*. reduced halo-acetones with (–)-DIP-chloride and (*R*)-Alpine-Borane.[143] The difference in stereochemical control for the reduction of α-fluoroacetone **38** to (*S*)-**39** was attributed to a chelating effect of the fluorine and the stronger Lewis acidic boron atom in (–)-DIP-chloride (Figure 24).[143]

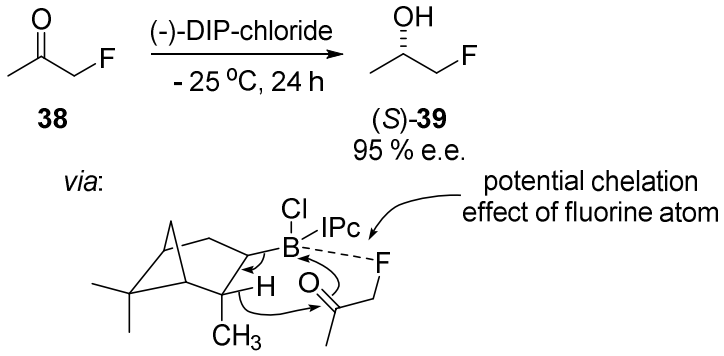


Figure 24 Reduction of α-fluoroacetone showing the potential fluorine-boron chelation.

We proposed that that the unexpected sense of asymmetric induction for the transfer hydrogenation of 2,2,2-trichloroacetophenone and 2,2,2-trifluoromethyl-alkyl ketones could be attributed to a potential electrostatic interaction between the electronegative halogens and the electropositive η^6-aryl C-H (Figure 25 and see **1.2**), which is discussed further in section **1.2**.

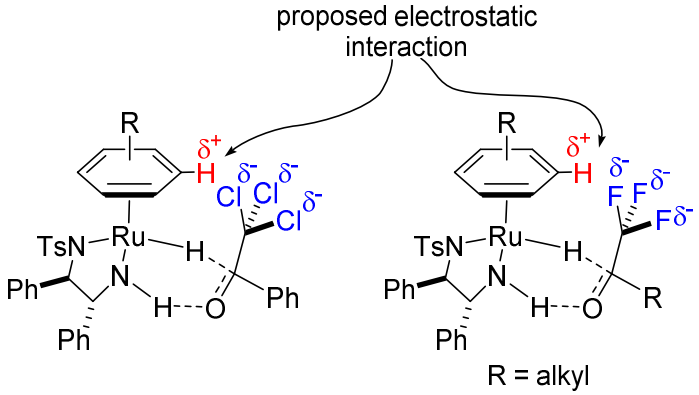
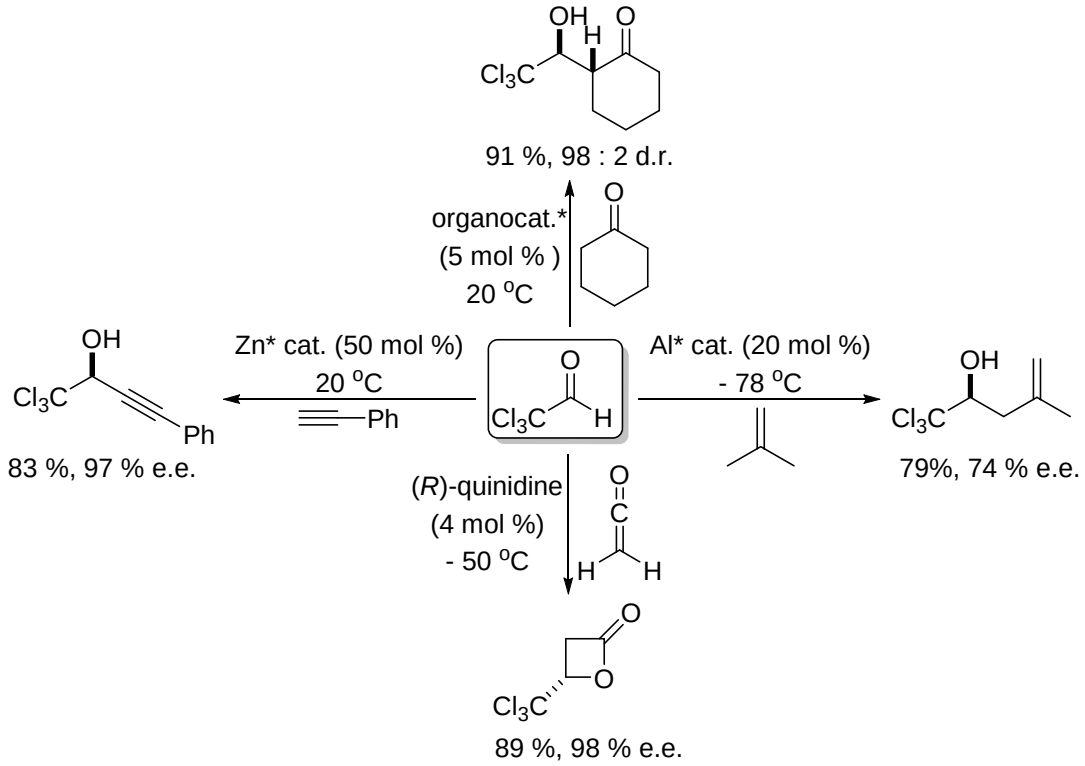


Figure 25 Proposed electrostatic interaction in the diastereomeric transition state for the reduction of 2,2,2-trichloroacetophenone and trifluoromethyl-alkyl ketones.

Comparing the α-chlorinated series in Table 3 with the fluorinated analogues in Scheme 31 it can be seen that there is a trend in stereoselectivity. As a chlorine or fluorine atom is successively added at the α-position of acetophenone the enantioselectivity decreases in both cases. Since 2,2,2-trichloroacetophenone is reduced with the opposite sense of induction compared with that of 2,2,2-trifluoroacetophenone it suggests that the trichloromethyl group is a more powerful directing group than trifluoromethyl in asymmetric transfer hydrogenation. Therefore, this suggested that we could potentially reduce alkyl-trichlorocarbinols in high enantiomeric excess.

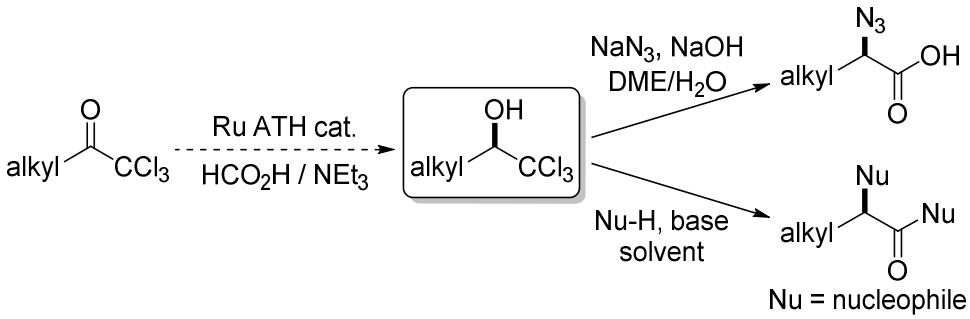
Other reported syntheses of enantiomerically enriched trichlorocarbinols, aside from the aforementioned reductions of trichloromethyl ketones using stoichiometric pinene-derived boranes[143, 156] or catalytically with the CBS-oxazoborolidine method,[136] include stereoselective additions to chloral (Scheme 32).[140, 167-172]



Scheme 32 Some stereoselective additions to chloral.

To determine the potential use of trichloromethyl moiety as a directing group in asymmetric transfer hydrogenation, we wanted to investigate the unreported reductions

of alkyl-trichloromethyl ketones (Scheme 33). The synthesised trichlorocarbinols are reactive intermediates in Corey-Link[136, 137] and Jocic-type reactions (Scheme 33).[173]

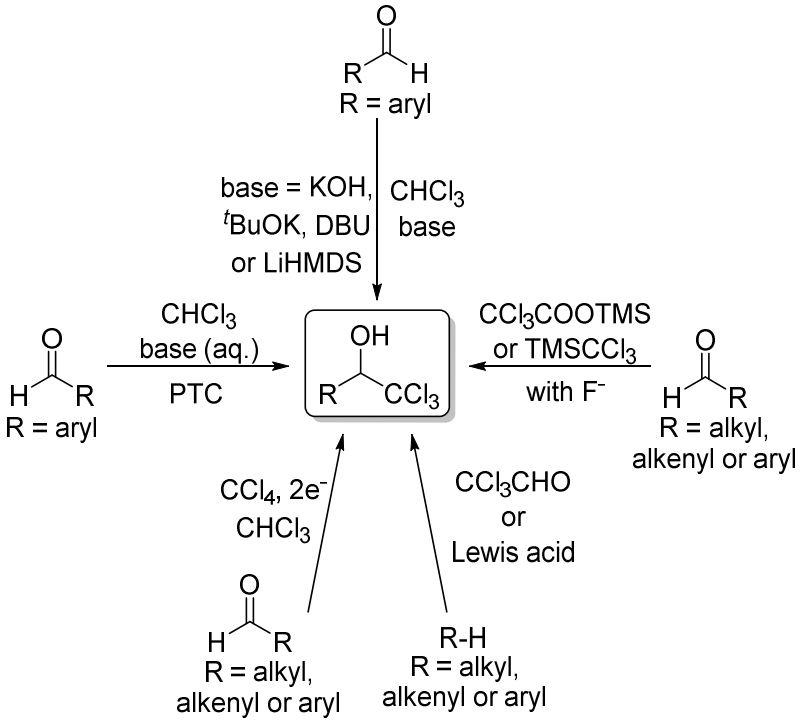


Scheme 33 Potential synthetic routes to be explored.

1.2 RESULTS AND DISCUSSION

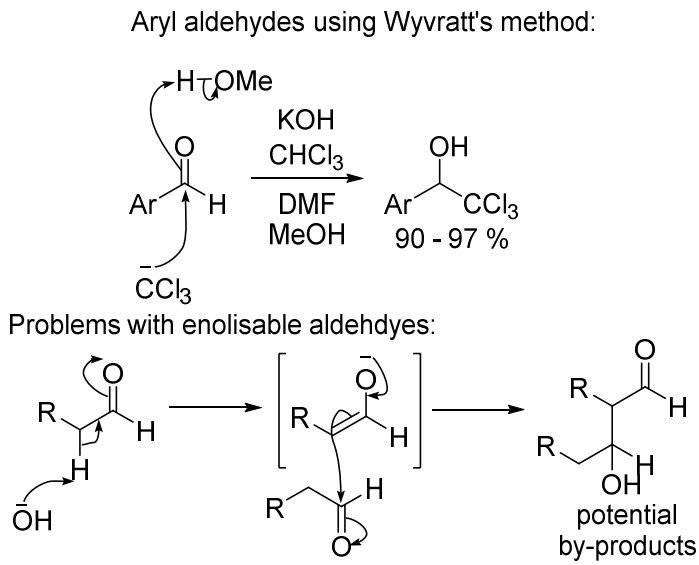
1.2.1 Literature Methods for the Synthesis of Racemic Trichlorocarbinols.

There are several reported methods for the synthesis of racemic trichlorocarbinols in the literature which are summarised in Scheme 34. Amongst the earliest methods was the addition of chloroform to aromatic aldehydes.[174] Since there have been many reported syntheses using these conditions.[175-185] Similar conditions with a phase transfer catalyst (PTC) have been reported.[186-190] Additions to chloral with a Lewis acid or aryl Grignard is another successful method for the synthesis of trichloromethyl carbinols.[191-196] Less common routes involve the electrochemical reduction of carbon tetrachloride[197, 198] and subsequent addition to aldehydes as well as the reactions of trimethylsilyl trichloroacetate[199] or (trichloromethyl)trimethylsilane[200, 201] with aldehydes in the presence of catalytic fluoride.



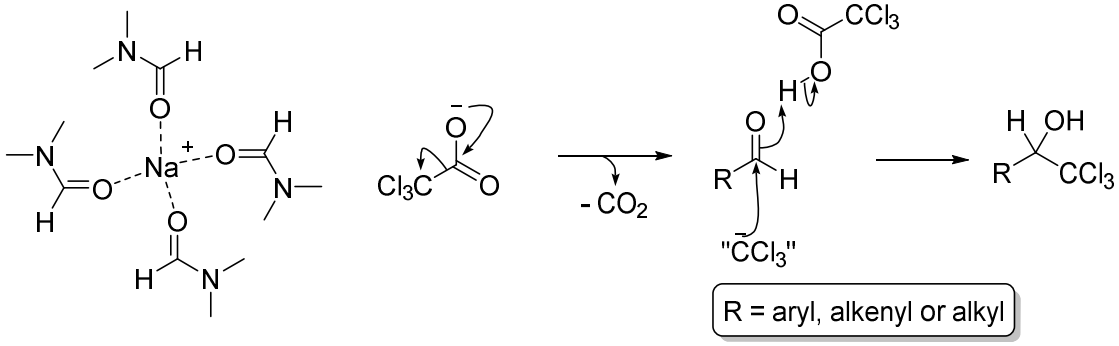
Scheme 34 Different early methods for the synthesis of racemic trichlorocarbinols.

Although some of these procedures are still followed there are two more recent methods that are preferentially used. These are the synthetic routes reported by Wyvratt[202] and that of Corey and Link.[137, 203] Wyvratt's method involves the deprotonation of chloroform in DMF and subsequent addition to an aromatic aldehyde (Scheme 35). A drawback to using this method is that only non-enolisable aldehydes can be used, meaning aliphatic aldehydes are not suitable. Furthermore, chloroform is an avoided solvent in scale-up.[204] However, due to the excellent yields generated from this method it is an ideal choice for the synthesis of trichloromethyl-aryl alcohols on small scale.



Scheme 35 Wyvratt's method for the synthesis of racemic trichlorocarbinols.

In 1992, Corey and Link reported a method that could be employed for all classes of aldehydes.[136, 137] This involves the reaction of an aldehyde with sodium trichloroacetate, buffered with trichloroacetic acid, in a coordinating solvent, such as DMF. Since most of the trichlorocarbinols we wanted to synthesise were aliphatic we opted to start the project using the more versatile method described by Corey and Link (Scheme 36).[136]

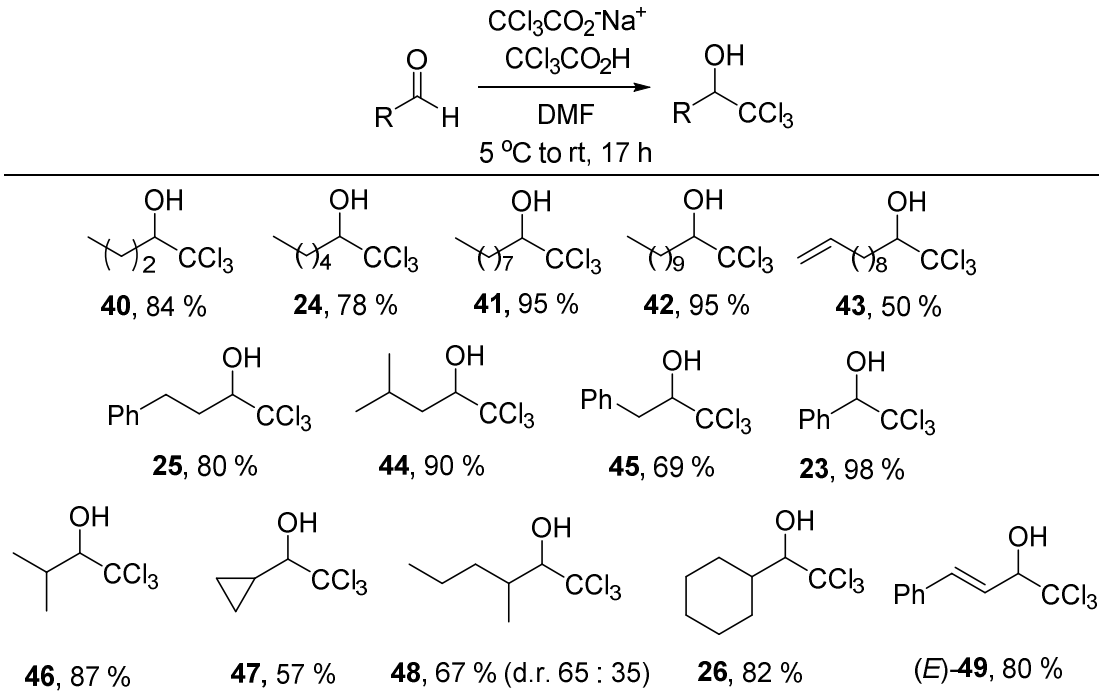


Scheme 36 Mechanism of trichlorocarbinol formation using Corey and Link's method.

The next section (**1.2.2**) has the experimental results that we obtained using the method in Scheme 36.

1.2.2 Experimental Results – Synthesis of Racemic Trichlorocarbinols and Trichloromethy Ketones.

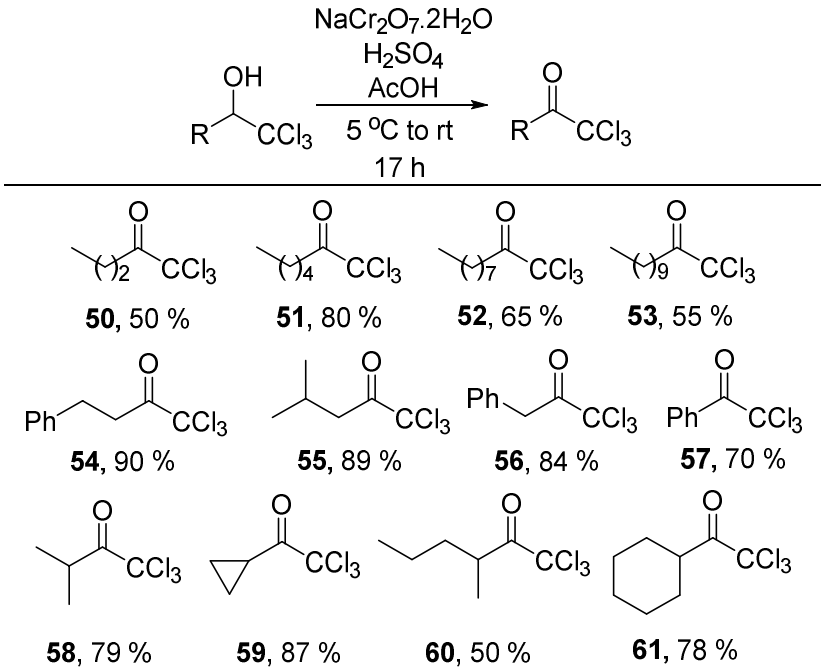
A wide variety of racemic trichlorocarbinols were synthesised in moderate to excellent yields using Corey and Link's method (Scheme 37).[136]



Scheme 37 Yields for trichlorocarbinols synthesised using Corey and Link's method.

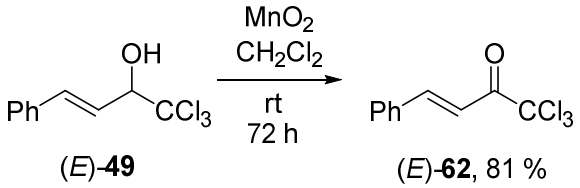
Reaction of 2-methylpentanal under these reaction conditions gave the corresponding trichloromethyl alcohol **48** in a 65 : 35 diastereomeric mixture, of which the configurations are unknown.

The next step was to synthesise the corresponding ketones of the reported racemic trichlorocarbinols shown in Scheme 37. Depending on the nature of the substrate a suitable oxidation method was selected. For the trichlorocarbinols containing no further potential reactive sites sodium dichromate was the chosen oxidant in acetic and sulfuric acid. Scheme 38 illustrates that the oxidations using this method proceeded smoothly to give the desired products in moderate to good yields.



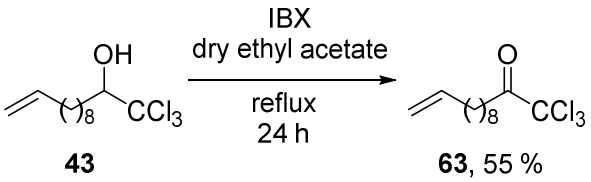
Scheme 38 Oxidation of unfunctionalised trichlorocarbinols using sodium dichromate.

For allylic trichlorocarbinols there are several oxidation methods reported in the literature. These include the Swern oxidation[203] and variants,[205] the use of the Dess-Martin periodinane (DMP)[205] and various chromium-containing oxidants such as PCC.[205-207] Due to its straightforward purification, manganese dioxide was the chosen oxidant for the synthesis of the α,β-unsaturated trichloromethyl ketone (*E*)-**57**. As shown in Scheme 39 the reaction of (*E*)-**49** with manganese dioxide in dichloromethane gave the desired product in a good 81 % yield.



Scheme 39 Oxidation of allylic trichlorocarbinols using manganese dioxide.

Furthermore, **43** was oxidised to **63** with 2-iodoxybenzoic acid (IBX) to ensure the alkene moiety was untouched in the reaction (Scheme 40).[208, 209]



Scheme 40 Oxidation of **43** with IBX.

Following the successful preparation of alkyl-trichloromethyl ketones in Scheme 38 and Scheme 39, and obtaining suitable splitting conditions of the racemic alcohols, using either chiral HPLC or GC, the asymmetric reductions could then be investigated.

1.2.3 Asymmetric Transfer Hydrogenations of Trichloromethyl Ketones.

Due to the vast success of ruthenium asymmetric transfer hydrogenation catalysts shown in Figure 26, we decided to test their enantioselection for the reduction of trichloromethyl ketones.[50, 87]

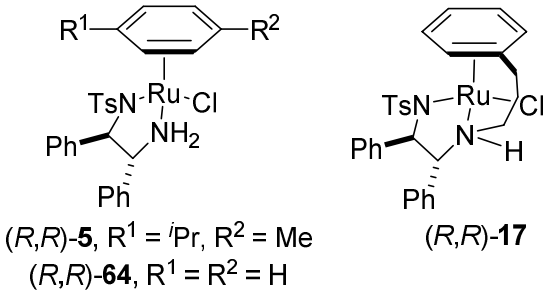
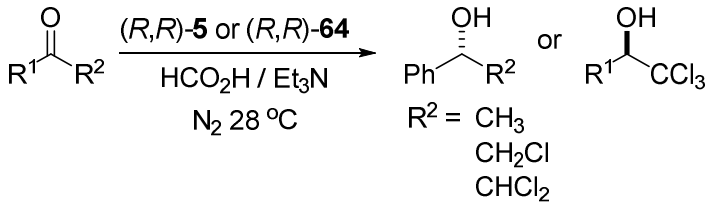


Figure 26 Ruthenium(II) asymmetric transfer hydrogenation catalysts.

Asymmetric transfer hydrogenations of a few alkyl-trichloromethyl ketones using Noyori's catalysts, (*R*,*R*)-**5** and (*R*,*R*)-**64**, gave their corresponding trichlorocarbinols in good yields and excellent enantiomeric excesses.[140] Table 4 shows these results together with the previously reported results (entries 1-4).



Entry	R^1	R^2	Catalyst	Yield	e.e.[a-c]	Alcohol
1	Ph	CH_3	(*R*,*R*)-**5**	95	95[a]	(*R*)-**20**[d]
2	Ph	CH_2Cl	(*R*,*R*)-**5**	77	96[a]	(*S*)-**21**[d]
3	Ph	$CHCl_2$	(*R*,*R*)-**5**	69	64[a]	(*S*)-**22**[d]
4	Ph	CCl_3	(*R*,*R*)-**5**	83	27[a]	(*R*)-**23**[d]
5	CH_3	CCl_3	(*R*,*R*)-**5**	85	98[b]	(*R*)-**65**[d]
6	CH_3	CCl_3	(*R*,*R*)-**64**	55	84[b]	(*R*)-**65**[d]
7	$CH_3(CH_2)_2$	CCl_3	(*R*,*R*)-**5**	84	95[c]	(*R*)-**40**[e]
8	$CH_3(CH_2)_2$	CCl_3	(*R*,*R*)-**64**	73	83[c]	(*R*)-**40**[e]
9	$Ph(CH_2)_2$	CCl_3	(*R*,*R*)-**5**	97	97[a]	(*R*)-**25**[d]
10	$Ph(CH_2)_2$	CCl_3	(*R*,*R*)-**64**	85	89[a]	(*R*)-**25**[d]

[a] Chiral HPLC. [b] Chiral GC on acetate derivative. [c] Chiral GC. [d] From sign of the rotation. [e] by analogy.

Table 4 Asymmetric transfer hydrogenation of chloroketones.

The *p*-cymene-based catalyst (*R*,*R*)-**5** produced the trichlorocarbinols with a higher degree of enantioselectivity (entries 5, 7 and 9) than the corresponding benzene-based catalyst (*R*,*R*)-**64** (entries 6, 8 and 10), as shown in Table 4.[140]

DFT calculations were performed by Dr David Fox using the same model catalyst system (with a simple aminoalcohol ligand) as used by Noyori and coworkers to analyse acetophenone[210] for ease of comparison.[140]

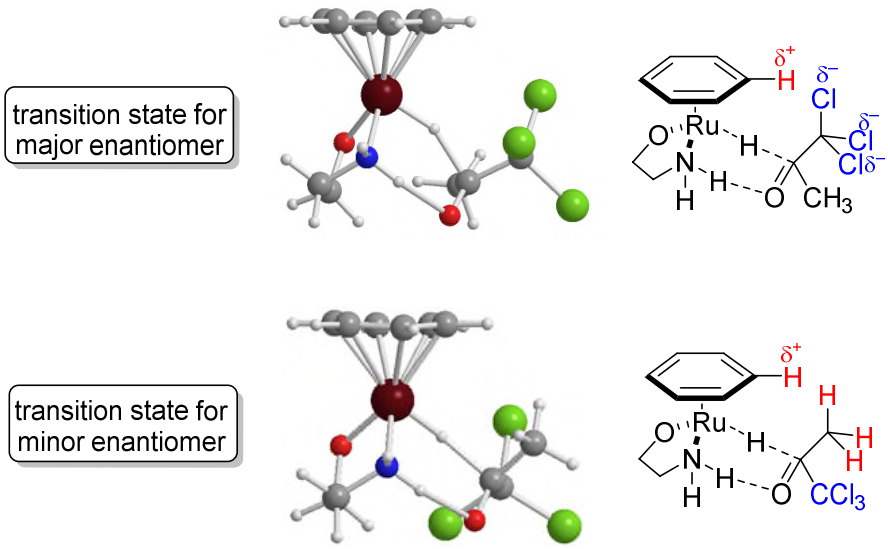


Figure 27 Calculated transition states by Fox for the major and minor enantiomers of alcohol with model catalyst analogous to that for acetophenone.

Transition states for reduction analogous to those for acetophenone were found (Figure 27). In the reduction of acetophenone the 'hydride-like' Ru-H hydrogen and 'proton-like' N-H hydrogen are delivered to the carbonyl in a highly concerted fashion.[211-214] In the case of 2,2,2-trichloroacetone the hydrogen transfers are significantly less concerted. From these calculations, an intermediate species in a very shallow potential well corresponding to an alkoxide intermediate was found. Such asynchronicity may be a result of the increased electrophilicity of 2,2,2-trichloroacetone compared to acetophenone, and reduced basicity of 2,2,2-trichloroacetone compared to acetophenone.[210] For the two diastereomeric pathways the 'hydride' product-determining transfer transition states are higher in energy than the corresponding proton transfers. The energy difference between two stereochemistry determining diastereomeric transition states **(**Figure 27) to be 13.7 kJ mol^{-1} (inc. ZPE) consistent with the major enantiomer, corresponding to 99 % e.e. at 28 $^{\circ}$C.[140]

The electron density map, provided by Anushka Joshi,[215] of the transition state for the major enantiomer (Figure 28) shows the potential electrostatic interaction, with red areas indicating electropositive areas and blue electronegative ones.

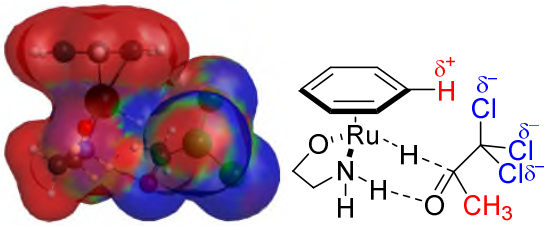


Figure 28 Electron density map of the transition state for the major enantiomer.

Figure 29 shows the electron density map of the transition state for the minor enantiomer and indicates that the electonegative chlorines are pointing away from the arene, supporting the evidence for a disfavoured interaction in the transition state.

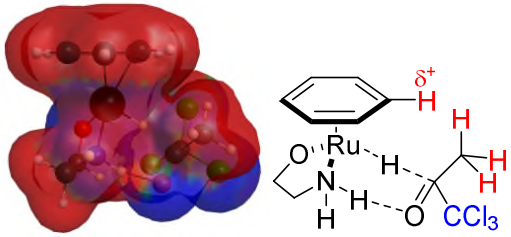


Figure 29 Electron density map of the transition state for the minor enantiomer.

There have been several computational studies reported in attempts to understand the factors which determine the enantiofacial control in asymmetric transfer hydrogenation reactions.[216] Andersson *et al.* suggested that the stereoselectivity of the transfer hydrogenations could arise from either attractive or repulsive forces between the substrate and the catalyst.[210] DFT calculations performed by van Leeuwen and coworkers indicate that steric hindrance is the main stereodetermining factor.[217] Contrastingly, calculations performed by Noyori and coworkers as well as isolation of the catalytic intermediates suggest that CH/π attractive interactions are more prominent.[86, 88, 214] DFT studies performed by Noyori,[88, 214] Ikariya,[212] Andersson[211] and van Leeuwen[217] point to the existence of a 6-membered concerted delivery of the Ru-H and N-H hydrogens to the prochiral ketone.[216] A further DFT study by Meijer and coworkers showed that methanol solvent molecules can play an active role in the

transfer hydrogenation of formaldehyde giving an 8-membered intermediate (Figure 30).[218]

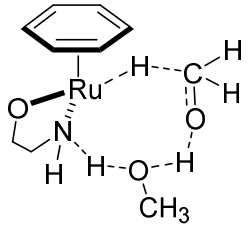
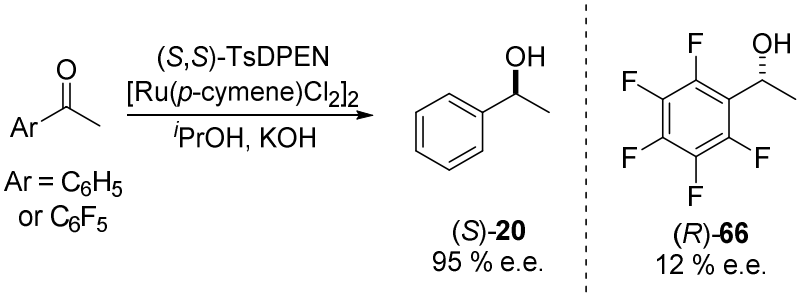


Figure 30 Proposed 8-membered intermediate for the transfer hydrogenation of formaldehyde.

Andersson and coworkers reported that 2,3,4,5,6-pentafluoroacetophenone is reduced to (*R*)-**66** with the opposite sense of induction compared with that of acetophenone, albeit in poor enantiomeric excess (Scheme 41).[210] This could suggest that there is potential electrostatic repulsion between the aryl moiety and the sulfonamide in the ligand.[210]



Scheme 41 Comparison of the asymmetric transfer hydrogenation of acetophenone and 2,3,4,5,6-pentafluoroacetophenone.

Andersson *et al*. concluded that the interaction between the η^6-arene ring and the aryl of the substrate seemed to be the major electrostatic interaction present in the amino alcohol system that they studied.[210] With this in mind a variety of alkyl-trichloromethyl ketones were reduced using *p*-cymene-based catalyst (*R*,*R*)-**5** and Wills' 'reverse-tethered' catalyst[92, 219, 220] (*R*,*R*)-**17**.

Figure 31 illustrates the scope of the trichloromethyl moiety as a directing group for ruthenium-catalysed transfer hydrogenation reactions.

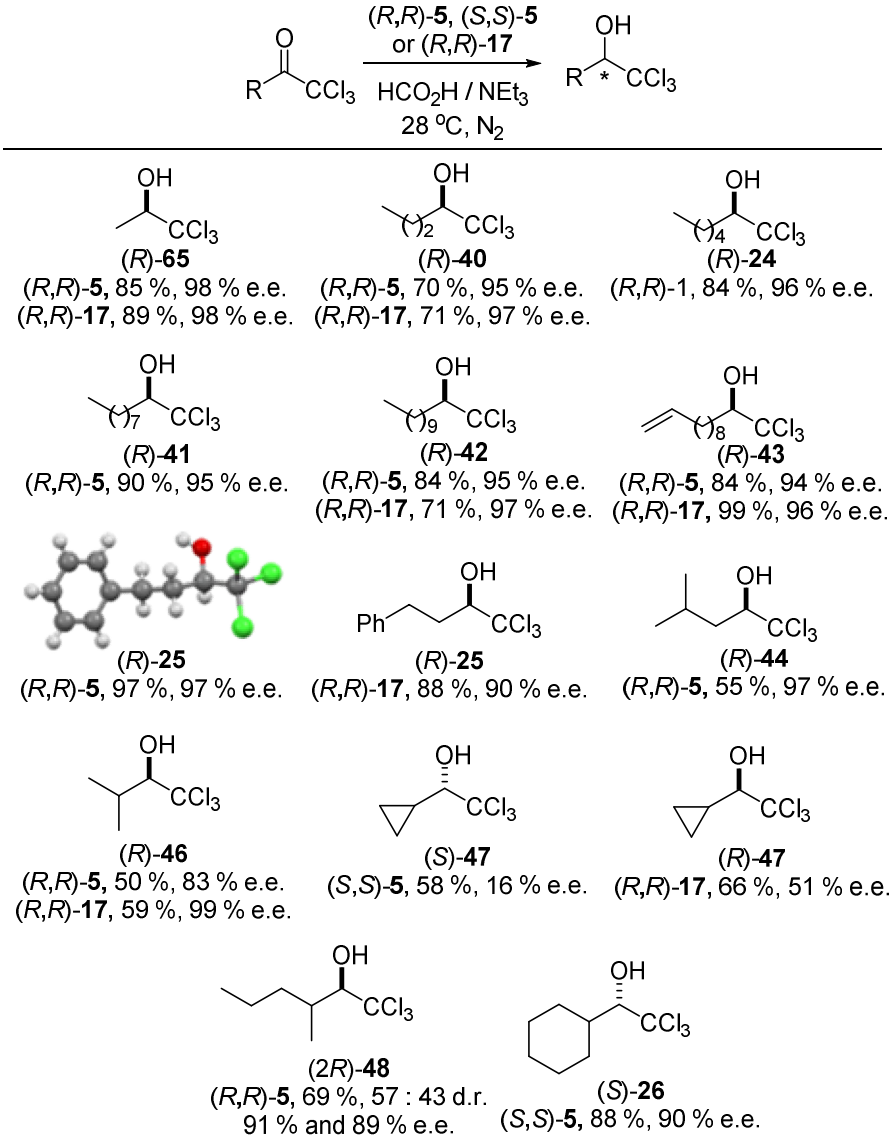
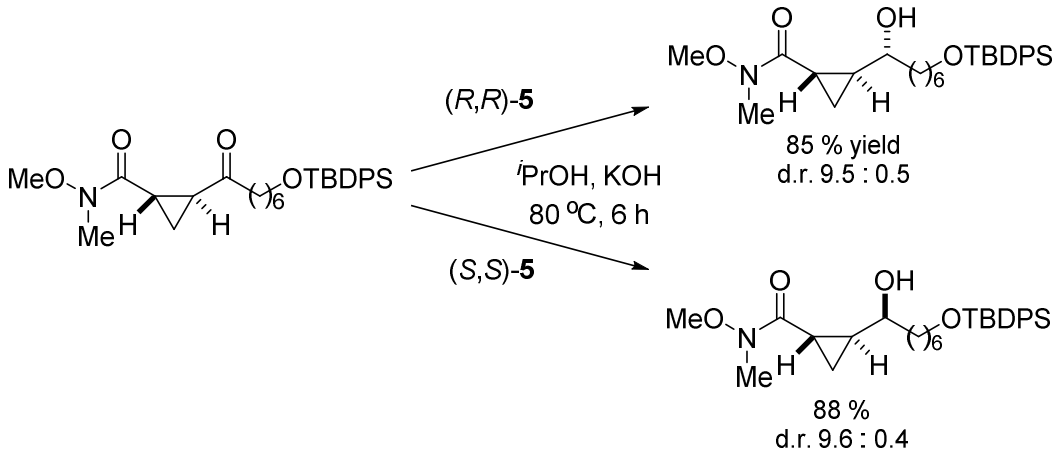


Figure 31 Asymmetric transfer hydrogenation of alkyl-trichloromethyl-ketones using (*R*,*R*)-**5**, (*S*,*S*)-**5** and (*R*,*R*)-**17**.

The trichlorocarbinols in Figure 31 were isolated in good yields and generally excellent enantiomeric excesses. The trichloromethyl ketones possessing a neighbouring methylene group, were reduced with excellent enantiofacial control with both catalysts, whereas those substituted at this position, showed slightly reduced enantioselectivities. The reduction of 1,1,1-trichloro-3-methylhexan-2-one **60** gives a diastereomeric mixture, of which the exact configurations are unknown. In accordance with the other reductions (Figure 31) the stereochemistry formed as a result of the stereoselective hydride addition has been assigned as (*R*). One notable exception in enantioselectivity is

the reduction of 2,2,2-trichloro-1-cyclopropylethan-1-one **59**, which gave the product in 16 % e.e. and 51 % e.e. (major enantiomer unknown) with (*S*,*S*)-**5** and (*R*,*R*)-**17** respectively. Alkyl-cyclopropyl ketones are reported to reduce with a high degree of enantioselectivity with the same sense of induction as alkyl-aryl ketones (Scheme 42).[221]



Scheme 42 Reduction of a cyclopropyl ketone with high diastereomeric excess with complete catalyst control.

The low selectivity for the product **47** in Figure 31 may therefore be due to closely competing diastereomeric reduction transition states (Figure 32).[140]

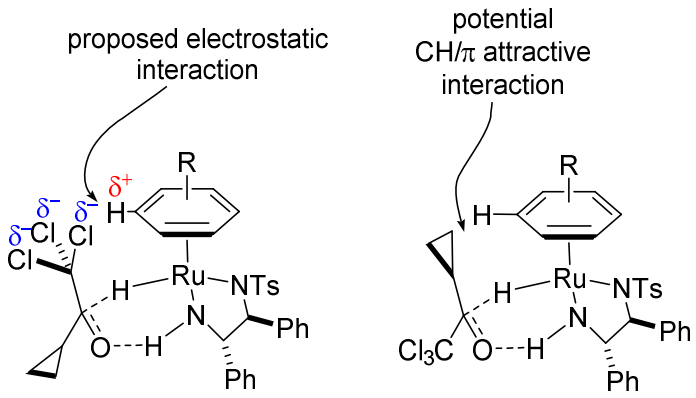
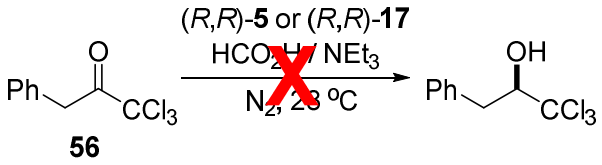


Figure 32 Proposed competing diastereomeric reduction transition states for the reduction of cyclopropyl ketone **59**.

Noticeably, when using 'reverse-tethered' catalyst (*R*,*R*)-**17** the degree of enantioselection for more substituted alkyl-trichloromethyl ketones improved. For example the enantiofacial control for the reduction of 1,1,1-trichloro-3-methylbutan-2-

one **58** significantly increased from 83 % e.e. to 99 % e.e (for (*R*)-**46**) and that of 2,2,2-trichloro-1-cyclopropylethan-1-one **59** increased from 16 % e.e. to 51 % e.e (for **47**). The absolute stereochemistry of **47** was confirmed from the X-ray crystal structure of (*R*)-2,2,2-trichloro-1-cyclopropylethyl 4-methylbenzenesulfonate (see Appendix 1).

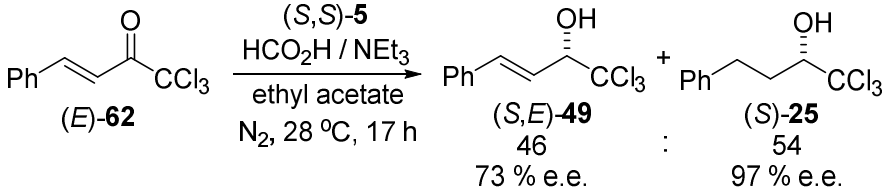
The asymmetric transfer hydrogenation of **56** (Scheme 43) was unsuccessful with neither starting material nor product recovered from the reaction mixture. It is thought that the highly acidic nature of the methylene hydrogens in the starting material coupled with the triethylamine present in the reaction conditions lead to decomposition of the starting material.



56

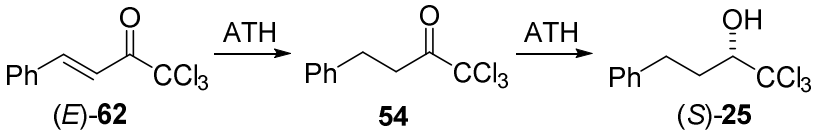
Scheme 43 ATH of **56** was unsuccessful with both (*R*,*R*)-**5** and (*R*,*R*)-**17**.

Additionally, the reduction of α,β-unsaturated ketone (*E*)-**62** gave two products; the desired allylic alcohol (*S*,*E*)-**49** in 73 % e.e. and the saturated alcohol (S)-**25** in 97 % e.e (Scheme 44).



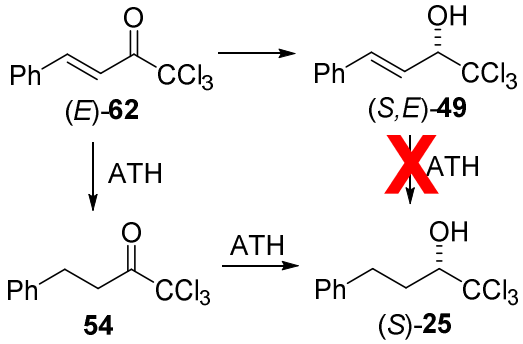
Scheme 44 ATH of acyclic α,β-unsaturated trichloroketone (*E*)-**62**.

In order for two products to be formed the reaction could proceed *via* three different pathways, which are discussed below. If the reaction proceeds *via* the route suggested in Scheme 45 then the two products should share the same enantiomeric excess since the reduction of the olefin does not affect the stereocentre. Since the two products of the reaction have different enantiomeric excesses then it is not possible for the reaction to proceed through this pathway.



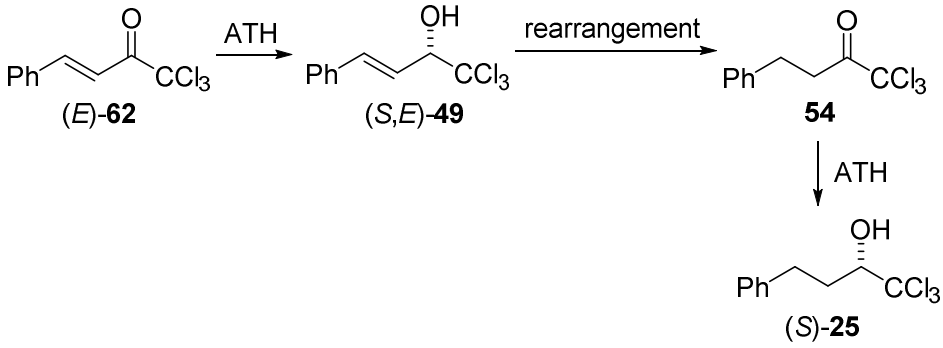
Scheme 45 Potential reaction pathway for the reduction of (*E*)-**62**.

In the pathway shown in Scheme 46 the reduction of the olefin in (*E*)-**62** is in competition with the reduction of the ketone functionality. This route suggests that once the ketone moiety has been reduced to form the enantiomerically enriched allylic alcohol (*S*,*E*)-**49** it is no longer feasible to be reduced. However, if the olefin in (*E*)-**62** is reduced first to form trichloromethyl ketone **54**, then it is possible for this to be reduced to form the enantiopure alcohol (*S*)-**25**. This route is viable since it is possible for each of the two products to have different enantiomeric excesses, which is observed (Scheme 44).



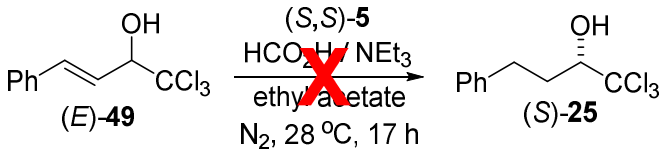
Scheme 46 Potential reaction pathway for the reduction of (*E*)-**62**.

Scheme 47 shows the ketone moiety is initially reduced to form the enantiopure allylic alcohol (*S*,*E*)-**49**, which can then undergo a rearrangement to form the saturated ketone **54**, which can then be reduced to form (*S*)-**25**.[222]



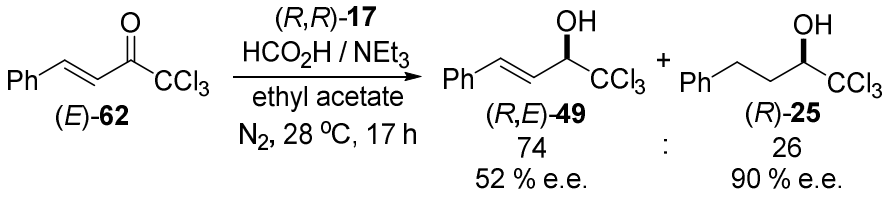
Scheme 47 Potential reaction pathway for the reduction of (*E*)-**62**.

In order to explore this potential pathway further racemic allylic alcohol (*E*)-**49** was subjected to the transfer hydrogenation conditions which gave completely unreacted starting material (Scheme 48). This confirmed that this is not involved in the reaction pathway.



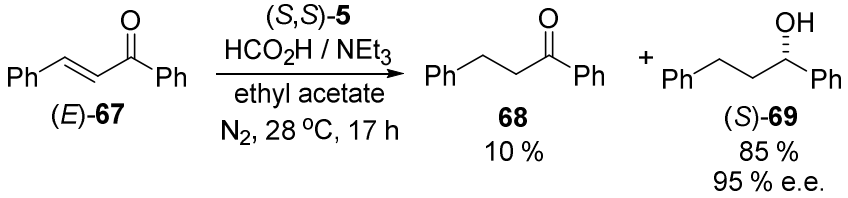
Scheme 48 Reaction of racemic (*E*)-**49** under transfer hydrogenation conditions gave only starting material.

Therefore, it is proposed that this transfer hydrogenation proceeds *via* the route in Scheme 46. The ratio of products shows that the reduction of olefin marginally outweighs that of the ketone moiety (Scheme 44). In order to investigate this further the reaction was repeated with 'reverse-tethered' catalyst (*R*,*R*)-**17** (Scheme 49).



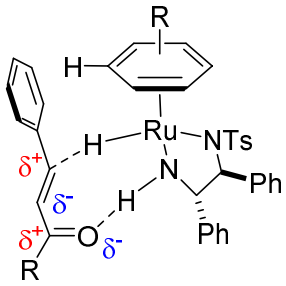
Scheme 49 Asymmetric transfer hydrogenation of (*E*)-**62** with (*R*,*R*)-**17**.

As with the *p*-cymene-based catalyst (*S*,*S*)-**5** the reaction with (*R*,*R*)-**17** gives two products of different enantioselectivities. Interestingly 'reverse-tethered' (*R*,*R*)-**17** gives better chemoselectivity for the reduction, though the enantiofacial control is poorer. To investigate the effect of the trichloromethyl moiety in these reactions it was replaced with a phenyl group. The asymmetric transfer hydrogenation of *trans*-chalcone (*E*)-**67** with (*S*,*S*)-**5** gave two products **68** and (*S*)-**69** (Scheme 50). The structures of **68** and (*S*)-**69** were confirmed from comparing the ^{1}H NMR spectra with that from the independently synthesised compounds.[223-226]



Scheme 50 Asymmetric transfer hydrogenation of *trans*-chalcone (*E*)-**67**.

For *trans*-chalcone (*E*)-**67** there is initially exclusive olefin reduction (Figure 33) to give the saturated ketone **68**, which can then be reduced to afford the enantiomerically enriched alcohol (*S*)-**69** in 85 % yield and 95 % e.e. (Scheme 50).



1,4-hydride addition
in the s-*cis* configuration

Figure 33 Hydrogenation 8-membered transition state of α,β-unsaturated ketones.

Comparing the products of the two reactions in Scheme 44 and Scheme 50 highlights that presence of the trichloromethyl group has an effect on the chemoselectivity of the reduction. The highly electronegative trichloromethyl moiety activates the 1,2-reduction in the α,β-unsaturated trichloroketone compared to the deactivated 1,2-reduction in *trans*-chalcone (*E*)-**67** (Figure 34).

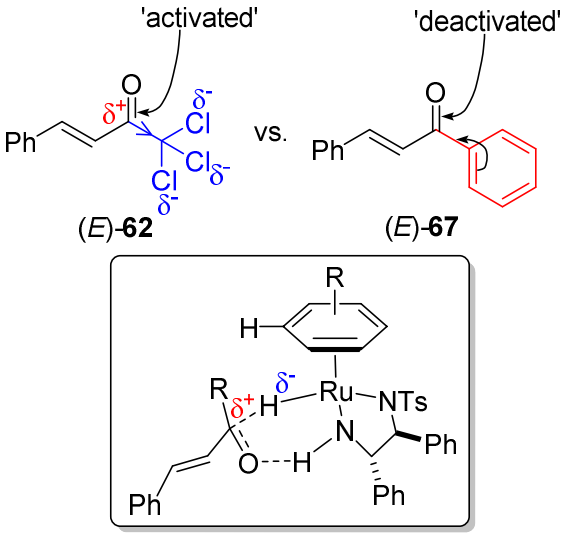


Figure 34 Hydrogenation transition state of α,β-unsaturated ketones (*E*)-**62** and (*E*)-**67**.

The asymmetric transfer hydrogenation of acyclic α,β-unsaturated trichloroketones were not as successful as their saturated analogues.

1.3 CONCLUSIONS

A general method for the synthesis of enantiomerically enriched trichlorocarbinols has been discussed in this chapter. The synthesis of racemic trichlorocarbinols was achieved using Corey and Link's conditions starting from their appropriate aldehydes. Subsequent oxidation of the racemic alcohols gave their corresponding trichloromethyl ketones. The ruthenium(II) catalysed asymmetric transfer hydrogenation of the trichloromethyl ketones gave the desired enantiopure trichlorocarbinols in excellent enantiomeric excesses, with a few exceptions. For example, the reduction of an α,β-unsaturated trichlorocarbinol gave a mixture of products with the desired alcohol formed in only moderate enantiomeric excess.

Trichlorocarbinols are versatile reactive intermediates and have been shown to react with a variety of nucleophiles in, generally racemic, Jocic-type reactions. We were particularly interested in converting some of the enantiomerically enriched

trichlorocarbinols into chiral drug building blocks using amine nucleophiles in the relatively unexplored stereospecific Jocic-type reactions (Chapter 2).

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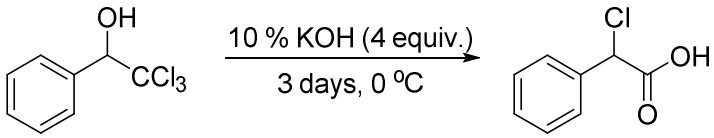
CHAPTER 2 – Jocic-type Reactions for the Synthesis of Amino-Amides.

2.1 INTRODUCTION

2.1.1 Jocic and Bargellini Reactions.

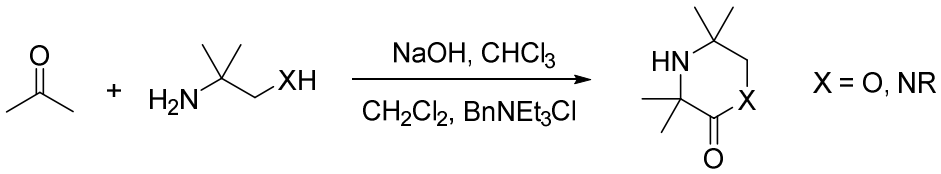
The Jocic reaction was reported in 1897 and describes the formation of α-chlorophenylacetic acid **70** from the reaction of 2,2,2-trichloro-1-phenylethan-1-ol **23** with potassium hydroxide on ice over three days (Scheme 51).[1, 2] Its tandem, one pot, nature provides an elegant and efficient route for the preparation of α-substituted acids.



23 **70**, 27 %

Scheme 51 The Jocic reaction.

A modified version of this reaction was reported in 1906 by Bargellini, which describes a route for the preparation of piperazin-2-ones and morpholin-2-ones from acetone (Scheme 52).[3] This transformation proceeds *via* the *in situ* formation of a trichloro-alkoxide species and subsequent reaction with a bis-nucleophile such as 2-amino-2-methyl-1-propanol or 1,2-diaminopropane.[4]



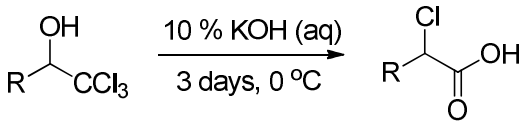
Scheme 52 Synthesis of piperazin-2-ones and morpholin-2-ones *via* Jocic-type chemistry.

Since there have been several reports using this method which involves the *in situ* deprotonation of chloroform and subsequent condensation with a ketone following the reaction with a given mono- or bis-nucleophile.[5-8] Much research has been invested

towards elucidating the mechanism by which this transformation proceeds, which will be discussed in section **2.1.2**.[2, 9-11]

2.1.2 Reaction Mechanism.

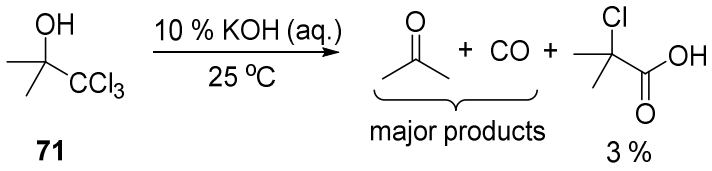
Reeve and coworkers performed mechanistic studies on the rearrangement of trichlorocarbinols to α-chloro acids.[2, 10] Upon investigating the scope of the Jocic reaction[1] it was found that a variety of secondary trichlorocarbinols would react to form their corresponding α-chloro acid generally in good yields (Table 5).



R	Yield %
$C(CH_3)_3$	78
CH_2CH_3	23
C_6H_5	60
p-Cl-C_6H_5	63
p-Br-C_6H_5	93
o-allyl-C_6H_5	46

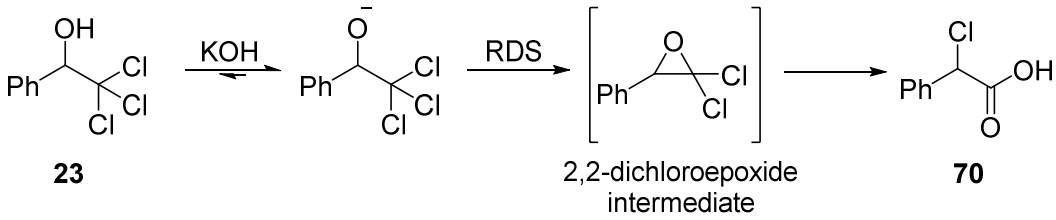
Table 5 Jocic reaction with secondary trichlorocarbinols.

Throughout their studies Reeve and coworkers noticed that 1,1,1-trichloro-2-methylpropan-2-ol **71** was unreactive at 0 ºC but would react slowly at 25 ºC, with the major product being acetone and carbon monoxide (Scheme 53).[2]



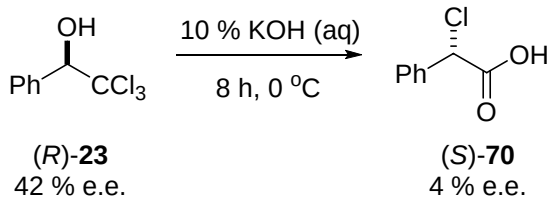
Scheme 53 Attempted Jocic reaction with tertiary trichlorocarbinol **71**.

Furthermore, the reaction with 2,2,2-trichloro-1-phenylethan-1-ol **23** was found to be 83 % intramolecular, which was determined from adding radioactive chloride into the reaction mixture and measuring the incorporation in the α-chloro acid product **71**.[2] Additionally, rate studies demonstrated the reaction of 2,2,2-trichloro-1-phenylethan-1-ol **23** with aqueous potassium hydroxide to be first order in alcohol and zero order in base. These results indicate that the formation of the 2,2-dichloroepoxide intermediate is the rate determining step (Scheme 54).[2]



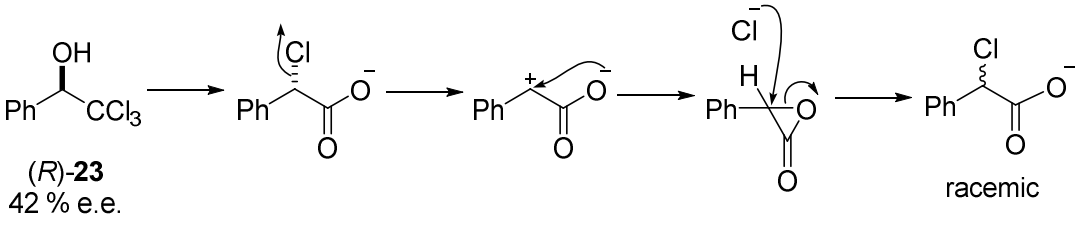
Scheme 54 Proposed route for the synthesis of α-chloro acids.

Stereochemistry studies on (*R*)-**23** (42 % e.e.) showed the α-chloro acid product to be 91 % racemised and 9 % inverted (Scheme 55).[2] (*R*)-**23** was obtained from the resolution of the quinine hydrogen succinate salt of 2,2,2-trichloro-1-phenylethan-1-ol **23**.[10]



Scheme 55 Jocic reaction with (*R*)-**23** (42 % e.e.).

From these results it was postulated that racemisation could occur from the reversible formation of an α-lactone intermediate, from the unimolecular ring formation by the acetate anion (Scheme 56).[10, 12]



Scheme 56 Proposed racemisation mechanism *via* an α-lactone intermediate.

Since the experiments with radioactive chloride suggested that 17 % of the reaction is intermolecular it was expected that 17 % of the product should have inverted stereochemistry.[2] It is thought that the much lower 9 % observed inverted stereochemistry comes from this 17 % of intermolecular formed product.[2]

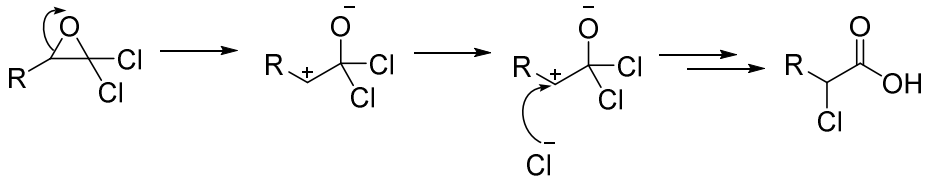
With all of the experimental observations made by Reeve a greater understanding of the mechanism could be achieved.[2] A suitable mechanism for this transformation should account for the following findings:

1. The requirement for a hydrogen on the α-carbon of the trichlorocarbinol.
2. The incorporation of 87 % unlabelled chlorine in the α-chloroacid product.
3. The requirement for aqueous, basic conditions.
4. Racemisation of the α-chloro acid product when enantiomeric enriched trichlorocarbinol is used.
5. No deuterium incorporation in the α-chloro acid product, when the reaction was carried out in deuterium oxide.

Reeve and coworkers postulated four different mechanisms that proceeded *via* a 2,2-dichloroepoxide intermediate:[2]

1. Carbonium ion mechanism.

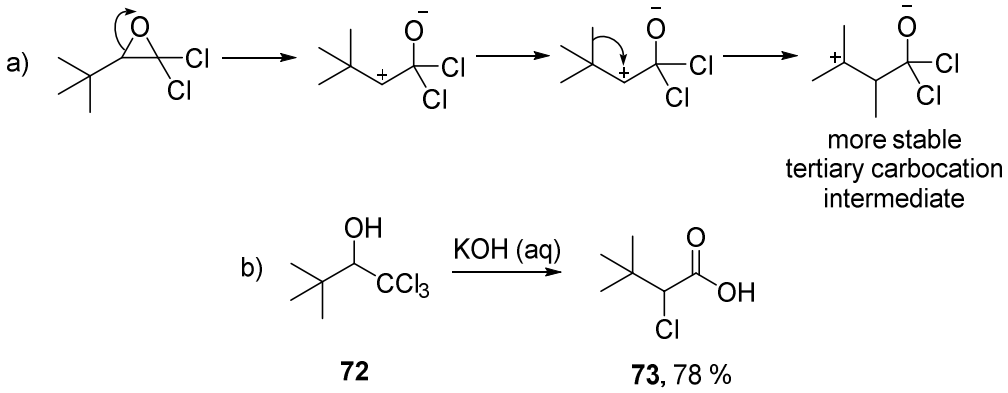
This pathway suggests that a carbocation is formed by the unimolecular ring opening of the 2,2-dichloroepoxide ring followed by attack of a chloride (Scheme 57).



Scheme 57 Proposed mechanism involving a carbonium ion.

This mechanism however fails to explain the observation that 2,2,2-trichloro-3,3-dimethylbutan-2-ol **72** (Table 5, 78 % yield) goes through the reaction unrearranged to

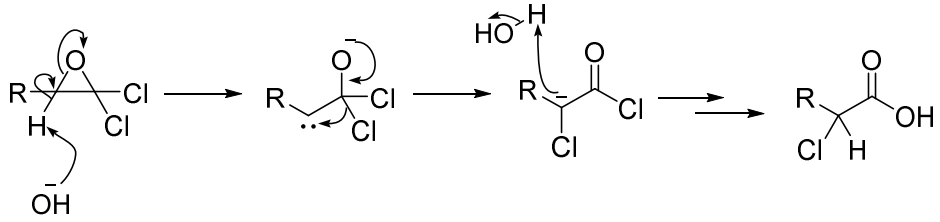
give **73** (Scheme 58). Other faults include the failed explanation of why base is required in the reaction and also why tertiary trichlorocarbinols are unreactive.



Scheme 58 a) Expected neopentyl rearrangement from 2,2-dichloroexpoide and b) observed reaction of **72**.

2. Carbene mechanism.

This mechanism suggests that the base in the reaction removes the hydrogen on the α-carbon atom, which subsequently opens the 2,2-dichloroepoxide and forms a carbene (Scheme 59). Following this the carbene abstracts one of the neighbouring chlorines to ultimately form the α-chloro acid.

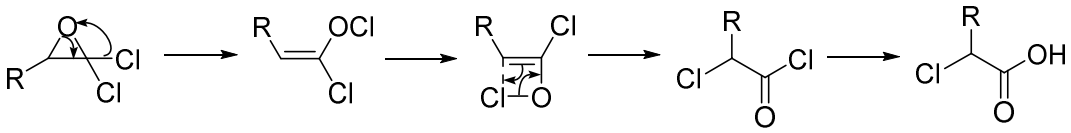


Scheme 59 Proposed mechanism *via* a carbene intermediate.

This mechanism explains why tertiary trichlorocarbinols are unreactive. Nevertheless, carrying out the reaction in deuterium oxide should give some deuterium incorporated in the α-chloro acid product, which is not observed.

3. Enol hypochlorite mechanism.

In this mechanism one of the chlorines in the 2,2-dichloroepoxide migrates to the oxygen atom to form an enol hypochlorite intermediate. This species then transfers the chlorine to the α-carbon *via* a *quasi* four-membered ring (Scheme 60).[2]

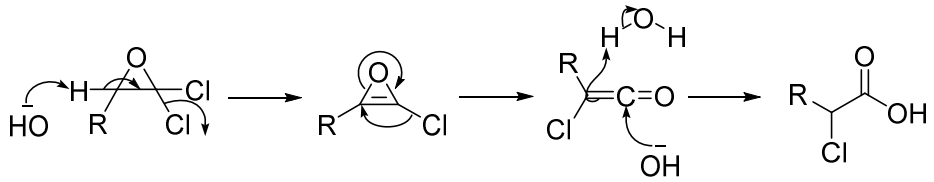


Scheme 60 Proposed mechanism involving an enol hypochlorite intermediate.

This mechanism fails to explain why the reaction with tertiary trichlorocarbinols is unsuccessful. Additionally, the suggested enol hypochlorite intermediate should be able to be trapped by a wide range of reducing agents, however attempted reactions with five different reducing agents were unsuccessful.[2]

4. Chlorooxirene mechanism.

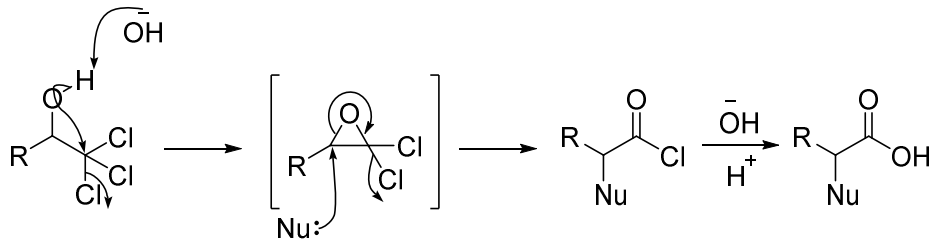
Oxirenes have been proposed as reaction intermediates,[13-15] but chlorooxirenes are unknown. They are thought to be highly strained unstable compounds.[13] The chlorooxirene intermediate is proposed to be formed by loss of HCl from the 2,2-dichloroepoxide (Scheme 61).



Scheme 61 Proposed mechanism *via* a chlorooxirene intermediate.

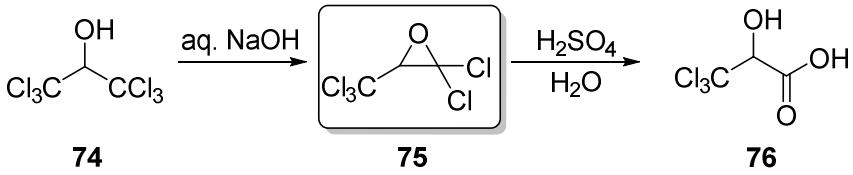
If this was the reaction mechanism the α-hydrogen would be replaced by deuterium if the reaction was carried out in deuterium oxide and this does not occur.[2]

All of the four mechanisms described above, involving a carbonium ion, carbene, enol hypochlorite or chlorooxirene, fail to comply completely with the experimental observations. The most commonly proposed mechanism[16] involves the *in situ* formation of a 2,2-dichloroepoxide intermediate and subsequent formation of an α-substituted acid chloride *via* an S_N2 reaction with a nucleophile (Scheme 62). The acid chloride is then converted into the corresponding α-substituted carboxylic acid.



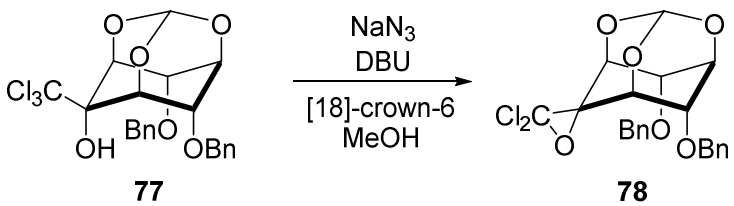
Scheme 62 Most commonly proposed mechanism for Jocic-type reactions.

In the case of the original Jocic reaction involving 2,2,2-trichloro-1-phenylethan-1-ol **23**, the suggested 2,2-dichloroepoxide intermediate is not isolatable.[17] In 1960, an intermediate of this nature was isolated, 2,2-dichloro-3-(trichloromethyl)oxirane **75** (Scheme 63).[18] This species was isolated from the reaction of 1,1,1,3,3,3-hexachloro-2-propanol **74** with aqueous sodium hydroxide. Further reaction of **75** with sulfuric acid afforded the α-hydroxy carboxylic acid 3,3,3-trichloro-2-hydroxypropanoic acid **76** (Scheme 63). This evidence suggests the existence of the 2,2-dichloroepoxide intermediate (Scheme 62).



Scheme 63 Isolation and subsequent reaction of 2,2-dichloro-3-(trichloromethyl)oxirane.

Furthermore, Scaffidi and coworkers managed to isolate two different 2,2-dichloroepoxide intermediates.[19] Both were isolated as a consequence of incomplete reactions, one of which being an attempted modified Corey-Link reaction as shown with the formation of **78** from **77** (Scheme 64).[19]



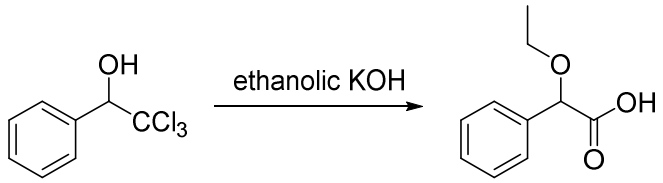
Scheme 64 An isolated 2,2-dichloroepoxide intermediate.

It was suggested that 'the trajectory of approach for a successful displacement by the azide ion is blocked in this rigid tricyclic system' and the structure was confirmed by a single-crystal X-ray structure investigation.[19] The isolation of these species explains the observed inversion of stereochemistry in the reaction and additionally the existence of the 2,2-dichloroepoxide intermediate (Scheme 62).

Since the discoveries of Jocic[1] and Bargellini[3] there have been several reports of this class of reaction using a wide variety of mono- and bis-nucleophiles.[16] These Jocic-type reactions will be discussed in detail, starting with oxygen nucleophiles (**2.1.3**).

2.1.3 Racemic Jocic-type Reactions with Oxygen Nucleophiles.

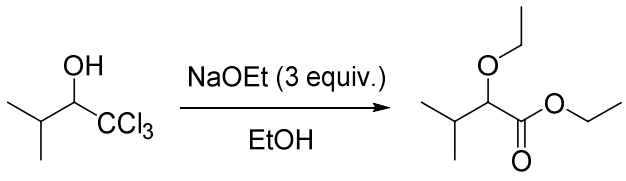
Following the report of the formation of 2-ethoxy-2-phenylacetic acid **79** from 2,2,2-trichloro-1-phenylethan-1-ol **23** (Scheme 65),[20] the scope of oxygen nucleophiles in Jocic-type reactions has been widely explored.



23 **79**

Scheme 65 First reported synthesis of an α-ethoxy acids.

Shortly after, the scope of these conditions was demonstrated as a range of α-alkoxy acids were prepared with alkyl trichlorocarbinols.[21] Esterification of these α-alkoxy acids to their corresponding α-alkoxy esters demonstrated a simple route for the synthesis of these class of compounds.[21] In 1947, as a consequence of the attempted preparation of 2-ethoxy-2-phenylacetic acid **79** the synthesis of ethyl 2-ethoxy-2-penylacetate **80** was reported (Scheme 66).[9] This provided a new route for the direct synthesis of α-alkoxy esters from trichlorocarbinols, removing the requirement of the esterification step.

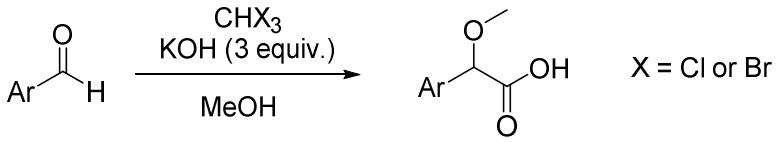


46 **80**, 72 %

Scheme 66 First preparation of α-ethoxy esters.

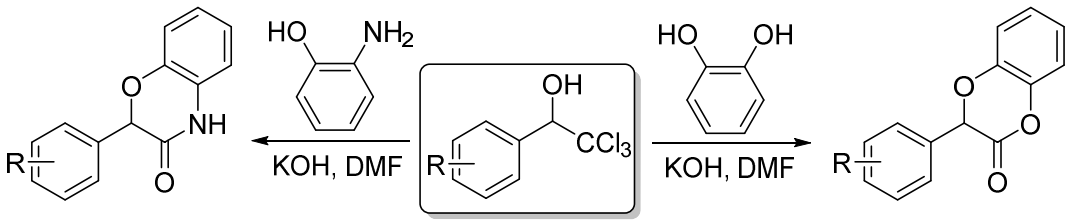
In 1950, Bergmann explored the scope of the previously reported chemistry[21] with reactions of substituted aryl trichlorocarbinols.[22] The successful synthesis of α-ethoxy and α-butoxyarylacetic acids, from the *o*-chloro, *m*-methoxy and *p*-methyl derivatives of 2,2,2-trichloro-1-phenylethan-1-ol **23**, were reported.[22] Additionally, α-methoxynaphthylacetic acids and derivatives were prepared from 2,2,2-trichloro-naphthyl alcohols using similar conditions.[23]

Reeve and coworkers made an advance in the field by the development of a 'one-step' synthesis for the preparation of α-methoxyarylacetic acids from aldehydes,[24, 25] which were previously unreactive using the conditions reported by Bargellini.[3] The procedure described by Reeve brings together the synthesis of trihalocarbinols and the Jocic-type chemistry of these substrates (Scheme 67). The scope of this chemistry was explored further by Reeve[24] and Benner,[25] where several more analogues were prepared.



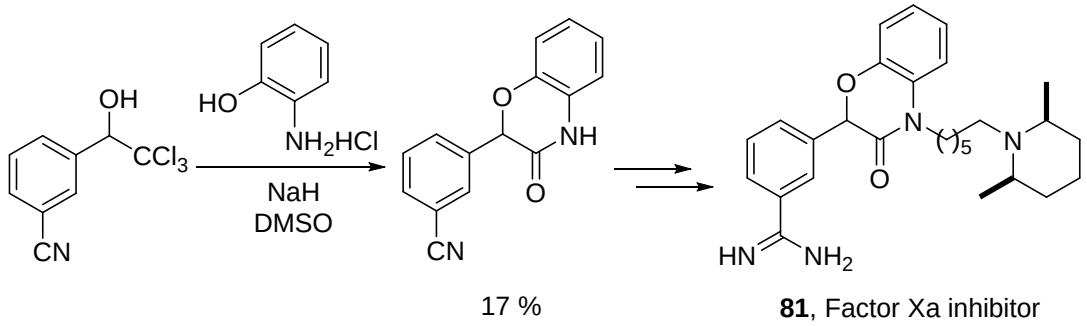
Scheme 67 'One-step' synthesis of *α*-methoxyarylacetic acids.

As previously described the reactions reported by Bargellini involve the formation of saturated heterocycles *via* the *in situ* trapping of the acid chloride species in the reaction.[3] An extension to the formation of saturated heterocycles using Jocic-type chemistry was reported by Gukasyan and coworkers in which 2-aminophenol and *o*-hydroxyphenol were reacted to form benzo[1,4]oxazin-3-ones and benzo[1,4]dioxin-3-ones (Scheme 68).[26]



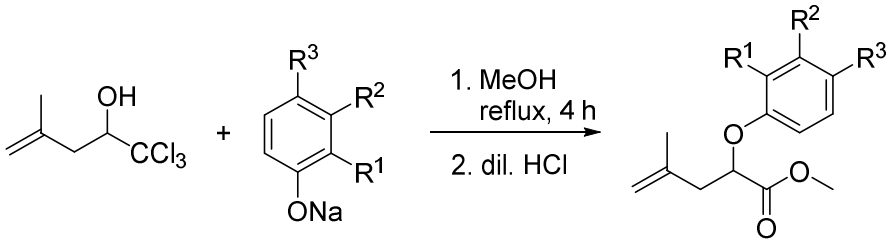
Scheme 68 Jocic-type reactions with 2-aminophenol and *o*-hydroxyphenol.

More recently, this methodology was used for the synthesis of a key intermediate of a novel Factor Xa inhibitor **81**,[27, 28] using modified conditions from the literature.[26]



Scheme 69 Synthesis of a key intermediate of a Factor Xa inhibitor using a Jocic-type reaction.

In 1991, Fechtel and coworkers used a variety of phenolate nucleophiles for the preparation of α-phenoxy methoxy esters (Table 6).[29]

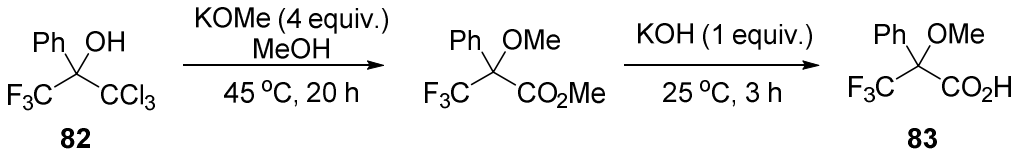


R^1	R^2	R^3	Yield %
H	H	H	41
H	H	CH_3	45
H	CH_3	H	27
CH_3	H	H	28
Cl	H	H	19
Cl	H	Cl	9

Table 6 Yields of Jocic-type reactions with substituted phenolate nucleophiles.

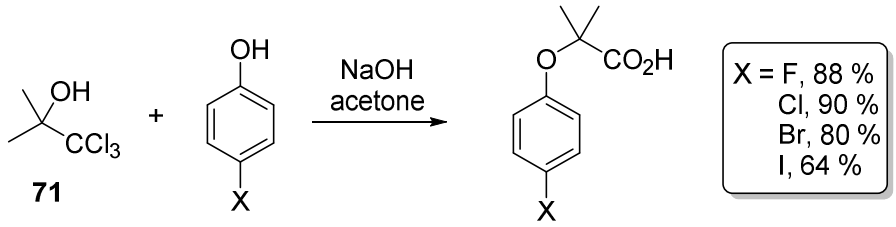
There are several examples of Jocic-type reactions of symmetrical and unsymmetrical tertiary trichlorocarbinols using oxygen nucleophiles in the literature.[30-34]

The transformation of 1,1,1-trichloro-3,3,3-trifluoropropan-2-ol **82** into α-(trifluoromethyl)-lactic acid precursors exploits Jocic-type chemistry.[35] This is particularly important since derivatives of α-(trifluoromethyl)lactic acid are highly desirable intermediates in the pharmaceutical industry and opto-electronic materials science.[30] Furthermore, the scope of this reaction in this field provided an industrial synthetic route for the synthesis of Mosher's acid **83** (Scheme 70), a valuable chiral derivatising agent, which can be used for enantiomeric excess determination and in some cases absolute stereochemistry assignment of chiral alcohols and amines.[36, 37]



Scheme 70 Jocic-type chemistry in the industrial synthesis of Mosher's acid.

The preparation of a series of 2-(4-halophenoxy)-2-methylpropanoic acids was reported in 1989 by reacting 1,1,1-trichloro-2-methyl-2-propanol **71** with sodium hydroxide and the relevant substituted phenol (Scheme 71).[31] Further examples of substituted and non-substituted α-(methoxyphenoxy)alkanoic acids are reported in the literature.[38-40]



Scheme 71 Synthesis of 2-(4-halophenoxy)-2-methylpropanoic acids.

The introduction of the *gem*-dimethyl[41] group as well as carboxylic acids[42] and esters[43] into drug molecules is particularly attractive. There are several examples in the literature where Jocic-type chemistry has been used to introduce these desirable functionalities into potential drug molecules. For example, a class of peroxisome proliferator-activated receptor (PPAR) related drugs have utilised this type of chemistry in synthesis of desired targets,[32, 33] which include Clofibric acid, Fenofibric acid and Bezofibrate (Figure 35).[34]

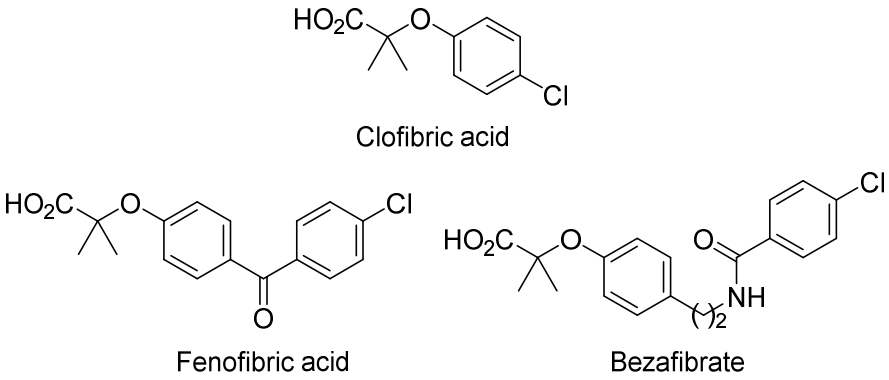
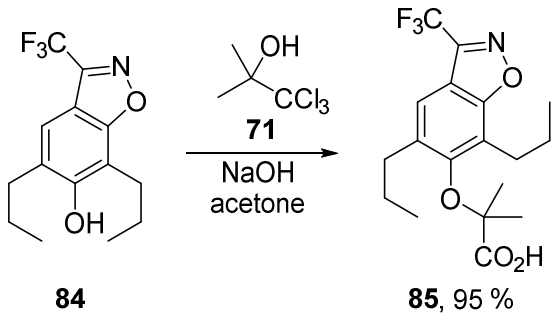


Figure 35 PPAR related drugs that use Jocic-type chemistry in their synthesis.

The synthesis of a dual PPAR α/γ agonist **85** by Merck illustrates the Jocic-reaction on kilogram scale giving the desired product in an excellent 95 % yield (Scheme 72).[44] The

reaction demonstrates use of a highly hindered phenol **84**, which highlights the scope and scalability of this class of reaction.

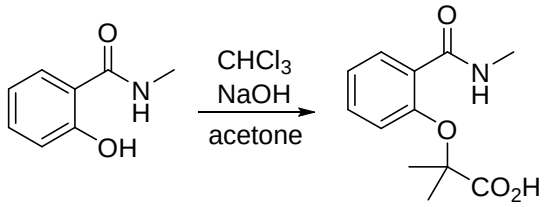


84 **85**, 95 %

Scheme 72 Jocic-type reaction using a highly hindered phenol.

There are several other reports of medicinally relevant compounds that make use of Jocic-type reactions with oxygen nucleophiles for the synthesis of key intermediates.[45-52]

In addition to the traditional Jocic-type conditions with oxygen nucleophiles starting from trichlorocarbinols, there are many reports using the 'one-pot' conditions described by Bargellini, starting with ketones.[3] Some examples include the initial development of Clofibrate-related drugs,[53] the synthesis of the antidepressant Efaproxiral sodium[54] and reactions on hindered macrocycles.[55] Further scope of this chemistry is shown by the synthesis of an *o*-substituted phenoxyalkanoic acid **87** in good yield from the reaction of 2-hydroxy-*N*-methylbenzamide **86** (Scheme 73).[56]



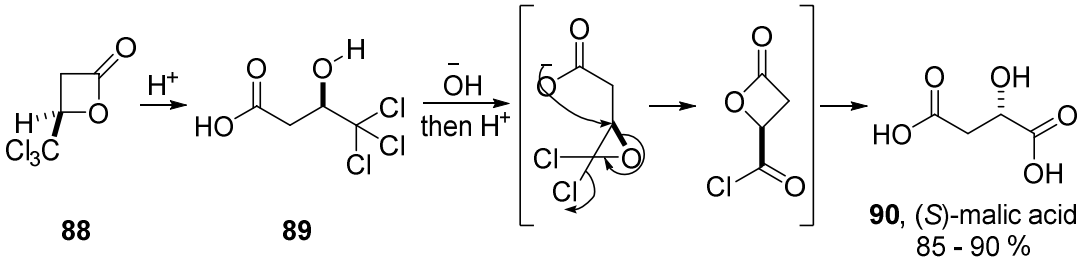
86 **87**, 62 %

Scheme 73 'One-pot' Jocic-type reactions of *o*-substituted phenols.

In addition to the many examples of racemic Jocic-type reactions with oxygen nucleophiles which have been discussed there are a few examples of stereospecific versions, which will be discussed in section **2.1.4**.

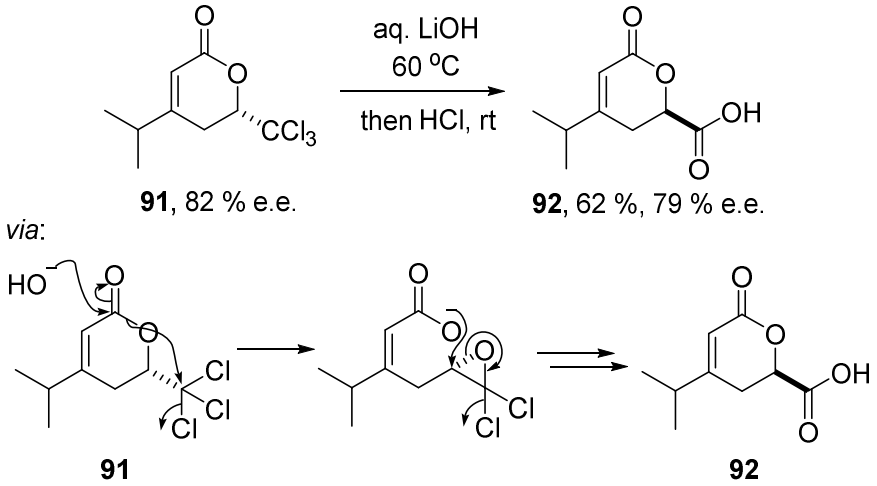
2.1.4 Stereospecific Jocic-type Reactions with Oxygen Nucleophiles.

Jocic-type reactions with both intra- and intermolecular oxygen nucleophiles have been documented. In 1984, the synthesis of (*S*)-malic acid **90** from (*R*)-4-(trichloromethyl)oxetan-2-one **88** *via* (*R*)-4,4,4-trichloro-3-hydroxybutanoic acid **89** was reported *via* a Jocic-type reaction involving an intramolecular carboxylate anion as a nucleophile (Scheme 74).[57]



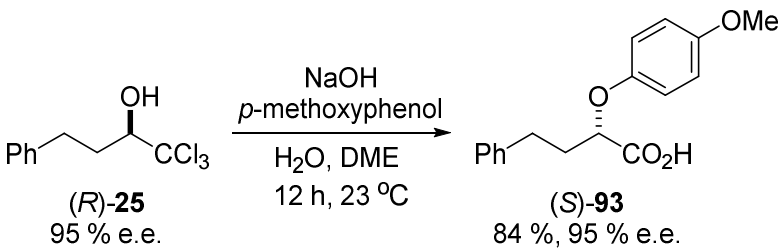
Scheme 74 Synthesis of (*S*)-malic acid *via* a Jocic-type reaction using an intramolecular oxygen nucleophile.

More recently, the transformation of a trichloromethyl-containing 6-membered lactone **91** into the corresponding carboxylic acid **92** is similarly thought to proceed *via* an S_N2 reaction with a ring-opened carboxylate anion nucleophile (Scheme 75).[58]



Scheme 75 Stereospecific Jocic-type reaction with intramolecular oxygen.

In 1992, Corey and Link reported the use of *p*-methoxyphenol as a nucleophile in an intermolecular stereospecific Jocic-type reaction for the synthesis of (*S*)-**93** (Scheme 76).[59] This same reaction was used again by Jiang and coworkers in 2004.[60]

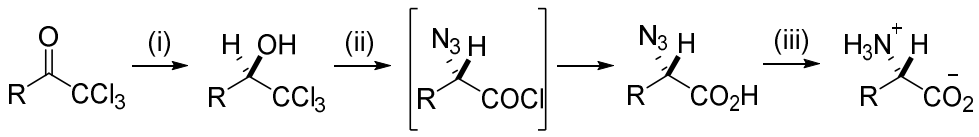


Scheme 76 Intermolecular stereospecific Jocic-type reaction with an oxygen nucleophile.

Aside from the use of *p*-methoxyphenol as described in Scheme 76 the use of intermolecular oxygen in stereospecific Jocic-type reactions is unexplored. In addition to oxygen nucleophiles in Jocic-type reactions, amongst the most well documented are nitrogen nucleophiles, which will be discussed in section **2.1.5**.

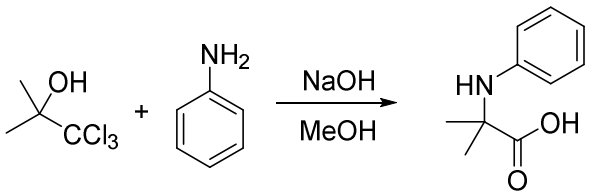
2.1.5 Racemic Jocic-type Reactions with Nitrogen Nucleophiles.

To date the reports of amine nucleophiles in Jocic-type reactions is limited, with one exception,[61] to racemic trichlorocarbinols as reactants. Since the discoveries of Corey and Link[59, 62] there have been several examples of stereospecific Jocic-type reactions with sodium azide (Scheme 77), which will be discussed in more detail in section **2.1.6**.[59, 62]



Scheme 77 Corey-Link synthesis of α-amino acids; (i) (*S*)-CBS, catecholborane (ii) NaOH, NaN_3, H_3O^+ (iii) 1 atm H_2, Pd/C.

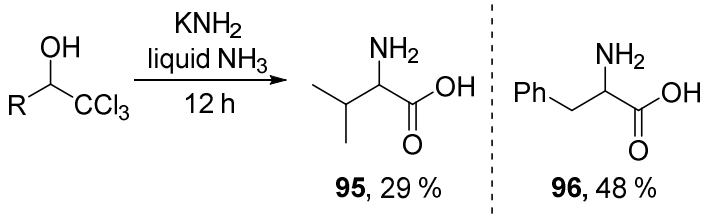
The majority of Jocic-type reactions with amine nucleophiles involve the use of tertiary trichlorocarbinols, using the traditional conditions,[63] or ketones, with Bargellini's method.[3] In 1929, Banti reported the synthesis of α-arylamino acid 2-methyl-2-(phenylamino)propanoic acid **94**, and other derivatives, from 2,2,2-trichloro-1-methylpropan-2-ol **71** and anilines (Scheme 78).[64]



71 **94**

Scheme 78 First use of acyclic amines as nucleophiles in Jocic-type reactions.

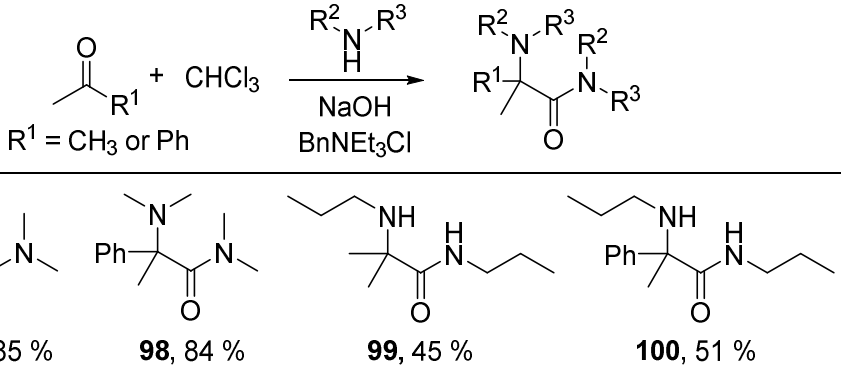
In 1964, Reeve and coworkers showed that racemic α-amino acids, such as **95** and **96**, could be prepared from the reaction of trichlorocarbinols and potassium amide in liquid ammonia (Scheme 79).[65] Since the yields of this process were not as high as those reported in Strecker synthesis this work was not explored further.[65]



95, 29 % **96**, 48 %

Scheme 79 Synthesis of racemic α-amino acids with KHN_2 in a Jocic-type reaction.

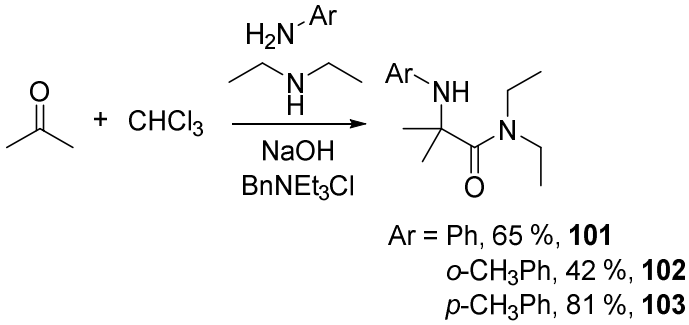
The first use of aliphatic amines as nucleophiles with Bargellini's conditions[3] was reported by Lai in 1980 with the synthesis of several racemic amino-amides (**97**-**100**, Scheme 80).[6]



97, 85 % **98**, 84 % **99**, 45 % **100**, 51 %

Scheme 80 Synthesis of racemic amino-amides with aliphatic amine nucleophiles in Jocic-type reactions.

Further studies with competing amine nucleophiles led to the discovery that the less nucleophilic aromatic amines ring-opened the 2,2-dichloroepoxide and the more nucleophilic aliphatic amines trapped the acid chloride intermediate (**101**-**103**).[6]



Scheme 81 Competitive reaction of aromatic and aliphatic amines in Jocic-type reactions.

The observed reactivity in Scheme 81 suggests that the reaction pathway is likely to proceed *via* a concerted process. The More O'Ferrall Jencks plot[66-70] (Figure 36) shows that the transition state **104** is stabilised by the delta negative nitrogen atom. When the amine is aromatic the negative charge can be stabilised over the ring, which explains why the aromatic amines react preferentially.

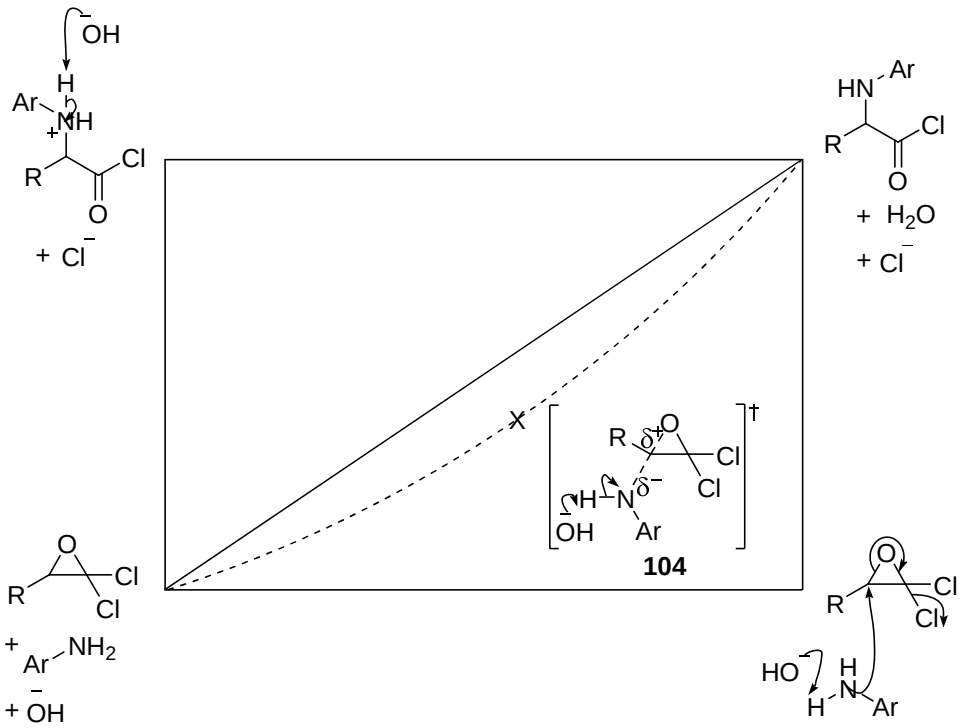
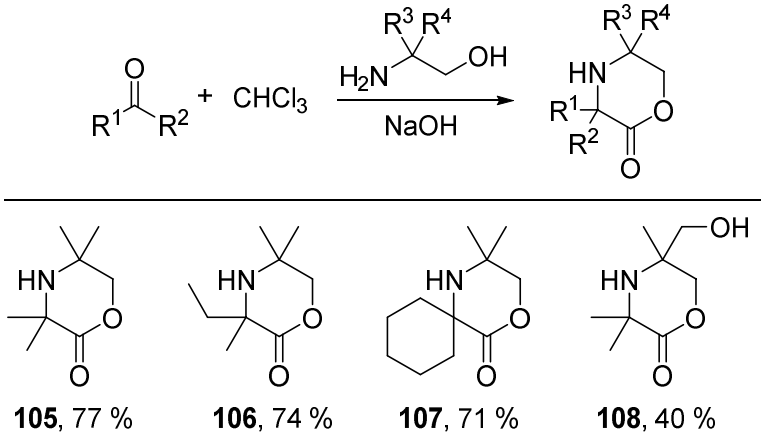


Figure 36 More O'Ferrall Jencks plot.

Shortly after, Lai investigated the reactivity and selectivity of 2,2-disubstituted-2-amino-ethanols using Bargellini's 'one-pot' conditions for the synthesis of the tetrasubstituted 6-membered rings.[8] It was shown that in each case the amine

functionality ring opened the 2,2-dichloroepoxide with the alcohol trapping the acid chloride to form morpholin-2-ones (**105**-**108**, Scheme 82).[8]



Scheme 82 Synthesis of tetrasubstituted morpholin-2-ones from amino-alcohol bis-nucleophiles.

In contrast to the analogous reaction with 2-aminophenol,[26] the chemoselectivity of the amino-alcohol bis-nucleophile has changed. As previously discussed in section **2.1.3** the reaction of 2,2,2-trichloro-1-arylethan-ols with 2-aminophenol gives benzo[1,4]dioxin-3-ones (Figure 37).[26]

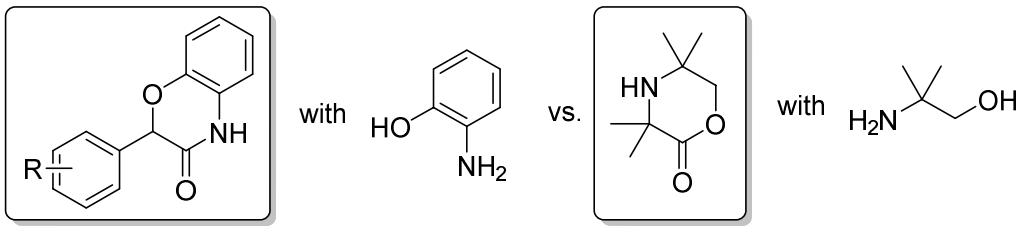
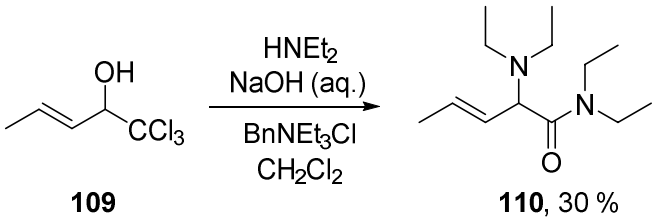


Figure 37 Difference in chemoselectivity of 2-aminophenol and 2,2,-dimethyl-2-aminoethanol in Jocic-type reactions.

Lai further demonstrated the scope of this method with the synthesis of octahydroquinoxalin-2(1*H*)-ones with cyclohexane-1,2-diamine and many 3,4-dihydroquinoxalin-2-ones with substituted *o*-phenylenediamines.[7, 8]

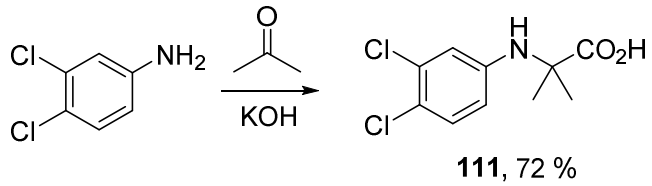
In 1986, the first report of a Jocic-type reaction with a secondary trichlorocarbinol **109** and an amine nucleophile, diethylamine, gave the corresponding amino-amide **110** in moderate yield (Scheme 83).[71]



Scheme 83 The first Jocic-type reaction with a secondary trichlorocarbinol.

Despite further investigations of aliphatic amines as nucleophiles being rare there have been several reports of aromatic amines as nucleophiles, namely substituted aniline derivatives.[72-75]

In a similar manner as discussed in section **2.1.3** the introduction of the *gem*-dimethyl moiety in drug candidates is also achievable with amine nucleophiles in Jocic-type reactions, for example the synthesis of a key intermediate **111** for serotonin receptor agonist candidates (Scheme 84).[76]

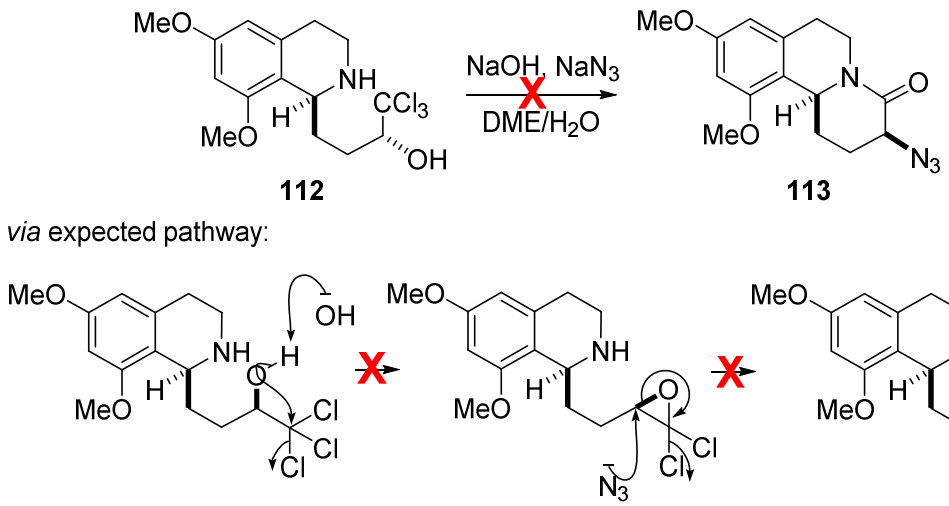


Scheme 84 Synthesis of an intermediate for serotonin receptor agonist candidates.

The only report of a stereospecific Jocic-type reaction with an amine nucleophile is discussed in section **2.1.6** as well as the many Corey-Link reactions[62] involving sodium azide.

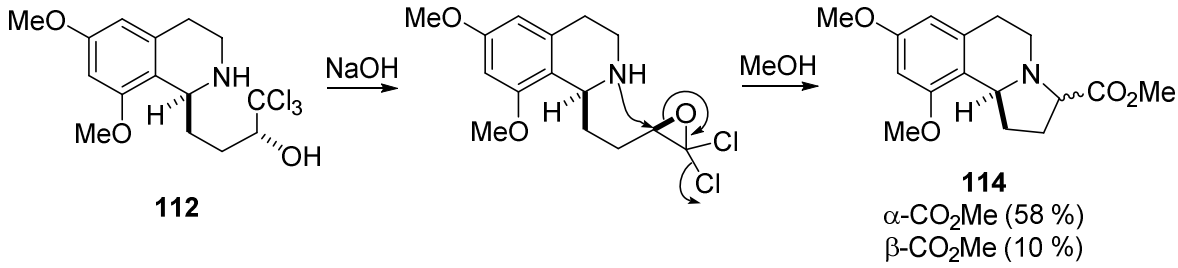
2.1.6 Stereospecific Jocic-type Reactions with Nitrogen Nucleophiles.

The scope of stereospecific Jocic-type reactions is limited to just one example in the literature, which involves an intramolecular secondary amine.[61] In fact this solitary report was an unintended transformation, which resulted from an unsuccessful Corey-Link reaction (Scheme 85).[62]



Scheme 85 Intended Jocic-type reaction using sodium azide.

The authors anticipated that the α-azido acid chloride, formed from **112**, could be trapped by the intramolecular secondary amine in order to form the desired α-azido lactam **113** (Scheme 85).[61] Surprisingly the secondary amine was the preferred nucleophile in the presence of sodium azide, which gave the unexpected 5-membered ring **114** (Scheme 86).[61]

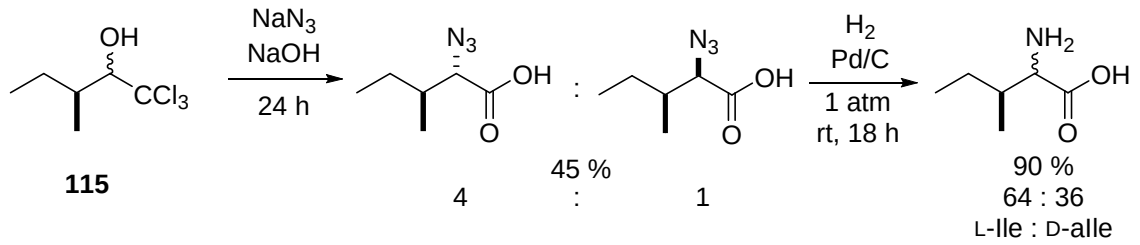


Scheme 86 Observed intramolecular stereospecific Jocic-type reaction with the secondary amine.

This issue was resolved by the Boc protection of the secondary amine, which removed the competition in the reaction allowing the azide to react and form the α-azido acid. Boc deprotection followed by coupling with the α-azido acid using diphenylphosphoryl azide gave the desired α-azido lactam.[61]

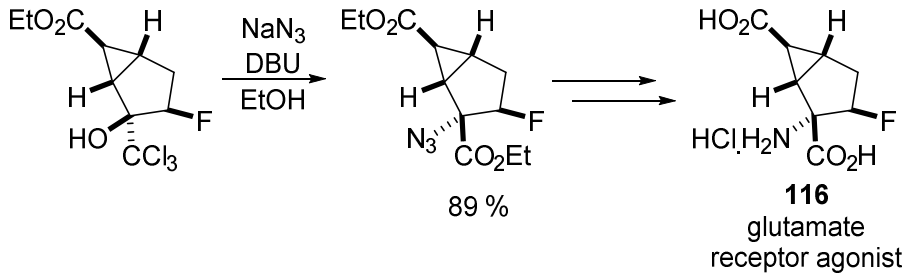
To date there are no reported stereospecific Jocic-type reactions using intermolecular amine nucleophiles.

In 1994, sodium azide was used in a Jocic-type reaction with **115** for the synthesis of a diastereomeric mixture of L-isoleucine and D-*allo*-isoleucine (Scheme 87).[77]



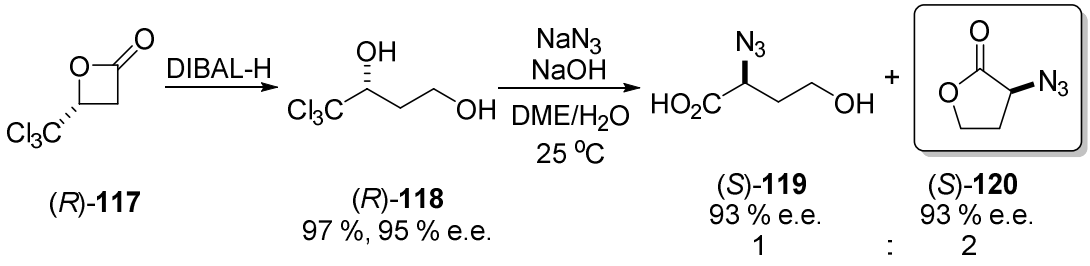
Scheme 87 Synthesis of L-isoleucine *via* a Jocic-type reaction with sodium azide.

In 2002, Pedregal and Prowse used modified Corey-Link conditions in step for the synthesis of a fluorinated (carboxycylcopropyl)glycine due to its potential as a glutamate receptor agonist **116** (Scheme 88).[78]



Scheme 88 Synthesis of a key medchem intermediate by a Corey-Link reaction.

In 2002, Romo and coworkers showed that an α-azido 5-membered lactone (*S*)-**120** could be formed from a stereospecific Jocic-type reaction of (*R*)-**118** with sodium azide.[79] Following the ring-opening of the 2,2-dichloroepoxide with azide the acid chloride intermediate is trapped with the intramolecular alcohol to form a mixture of products (*S*)-**119** and (*S*)-**120** (Scheme 89).

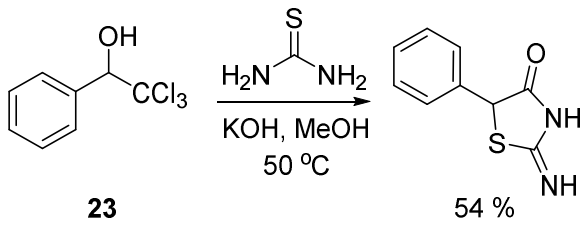


Scheme 89 Corey-Link reaction on a trichloromethyl containing β-lactone.

Since, there have been several other reports of stereospecific Jocic-type reactions using sodium azide.[80-85] The much rarer nucleophiles used in Jocic-type reactions include sulfur (**2.1.7**), selenium (**2.1.8**), carbon (**2.1.9**), fluorine (**2.1.10**) and hydrogen (**2.1.11**).

2.1.7 Jocic-type Reactions with Sulfur Nucleophiles.

In 1967, Reeve and Nees widened the scope of Jocic-type reactions with the use of sulphur nucleophiles.[86] Successful reactions with thiourea (Scheme 90) and potassium methyl xanthate were reported.[86] Competition experiments showed that thiourea was the best nucleophile for Jocic-type reactions, with respect to methoxide and potassium amide.[86]



Scheme 90 Use of thiourea as a bis-nucleophile in a Jocic-type reaction.

Due to the diverse biological activities of compounds bearing the 2-imino-4-thiazolinone core,[87-89] Blanchet and Zhu reported the synthesis of a variety of related analogues using a modified version of Reeve's conditions (Figure 38).[86, 90] Optimal conditions required treatment of a mixture of a trichlorocarbinols and thiourea with four equivalents of NaOH in DME/H_2O.[16, 90]

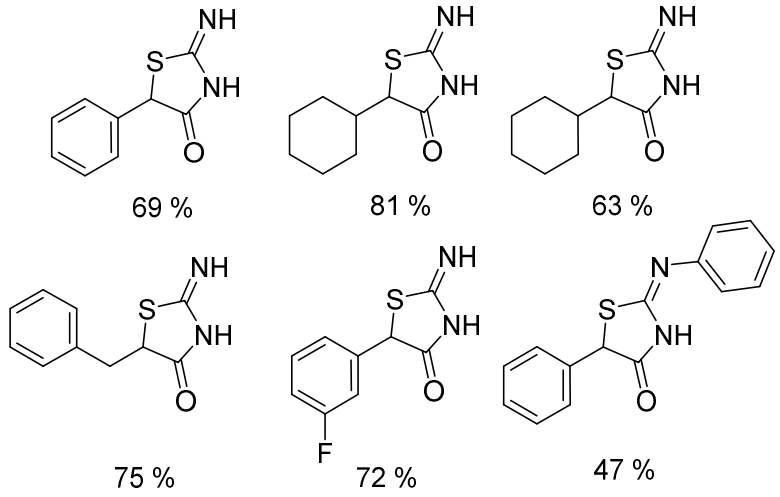
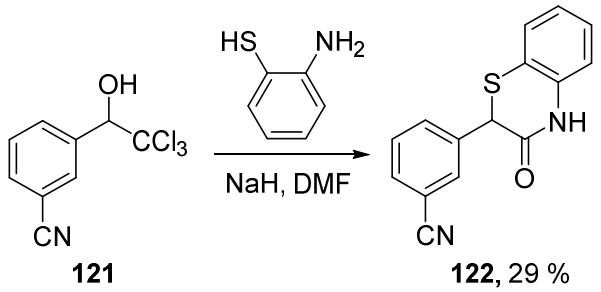


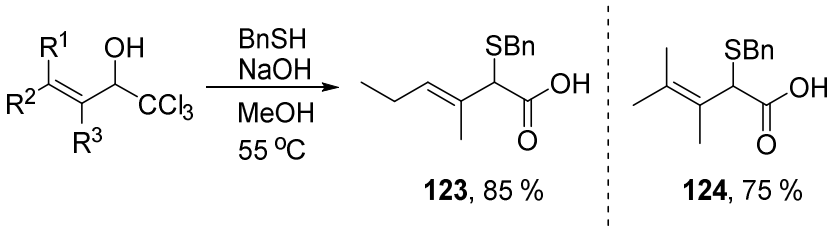
Figure 38 Some 2-imino-4- thiazolidinones synthesised *via* Jocic-type reactions.

Expanding the scope of sulfur nucleophiles in Jocic-type reactions, Willardsen and coworkers demonstrated that sulfur would preferentially ring-open the 2,2-dichloroepoxide instead of nitrogen from the reaction of 2,2,2-trichloro-1-*m*-cyanophenylethano-1-ol **121** with 2-aminothiophenol (Scheme 91).[91] In fact the nitrogen in the bis-nucleophile performed the intramolecular ring closure, which ultimately formed the desired thiomorpholin-3-one **122** (Scheme 91).



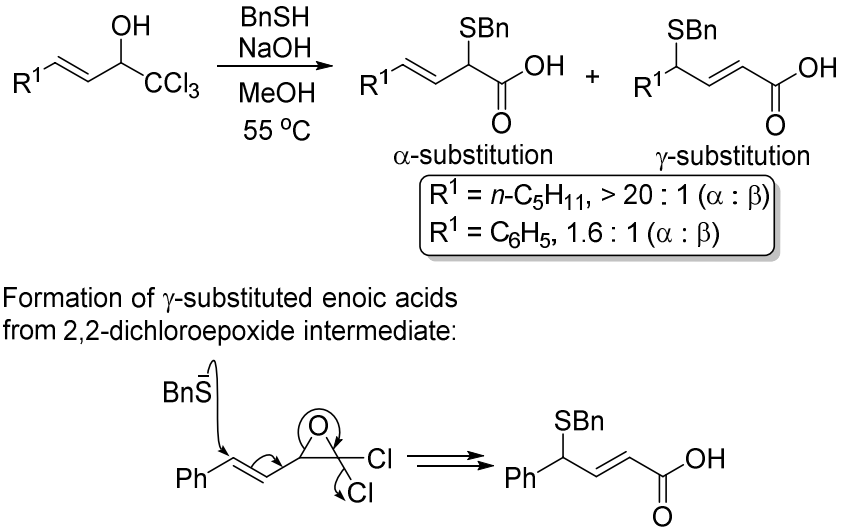
Scheme 91 Synthesis of thiomorpholin-3-one **122** using a Jocic-type reaction with 2-aminothiophenol.

Snowden and Shamshina explored the regioselectivity of the additions of sulfur nucleophiles to tri- and di-substituted alkenyl trichlorocarbinols.[92] Addition of phenylmethanethiol to trisubstituted versions led to exclusively α-substituted enoic acids **123** and **124** in good yields (Scheme 92).



Scheme 92 Synthesis of α-sulfur-substituted enoic acids *via* a Jocic-type reaction.

Using identical conditions, addition of phenylmethanethiol to disubstituted alkenyl 2,2,2-trichloromethyl alcohols gave a mixture of α- and γ-enoic acids. The nature of the terminal substituent determined the overall selectivity.[92] When R^1 was an alkyl chain the product was formed was predominantly the α-substituted enoic acid and when R^1 was phenyl the ratio of α- to γ-substituted enoic acid become much closer at 1.6 : 1 respectively (Scheme 93).

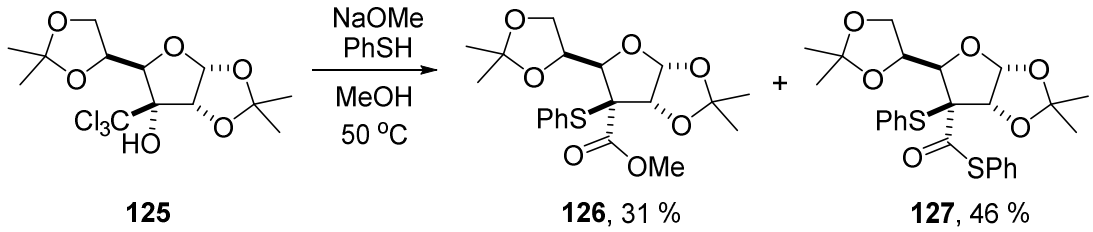


Scheme 93 Formation of α- and γ-sulfur-substituted enoic acids and mechanism for the γ-substituted enoic acid derivative.

As shown in this section there are very few reports of sulfur nucleophiles in racemic Jocic-type reactions and in fact there is just one example of a stereospecific Jocic-type reaction in the literature.[19]

The solitary example of a stereospecific Jocic-type reaction of **125** with a sulfur nucleophile was reported by Scaffidi and coworkers in 2006.[19] A mixture of products was isolated; the desired methoxy ester **126** and the corresponding thioester **127**

(Scheme 94). Further experimental investigation showed that the methoxy ester **126** was in fact formed first and subsequent trans-esterification with the remaining thiophenol led to the formation of the thioester **127**.[19]



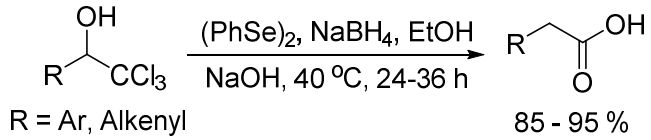
125 **126**, 31 % **127**, 46 %

Scheme 94 Use of thiophenol as a sulfur nucleophile in a Jocic-type reaction.

In addition to their work on Jocic-type reactions with sulfur nucleophiles (Scheme 92 and Scheme 93), the scope of a selenium nucleophile has was explored by Snowden and coworkers for one-carbon homologations (**2.1.8**).[16, 93-95]

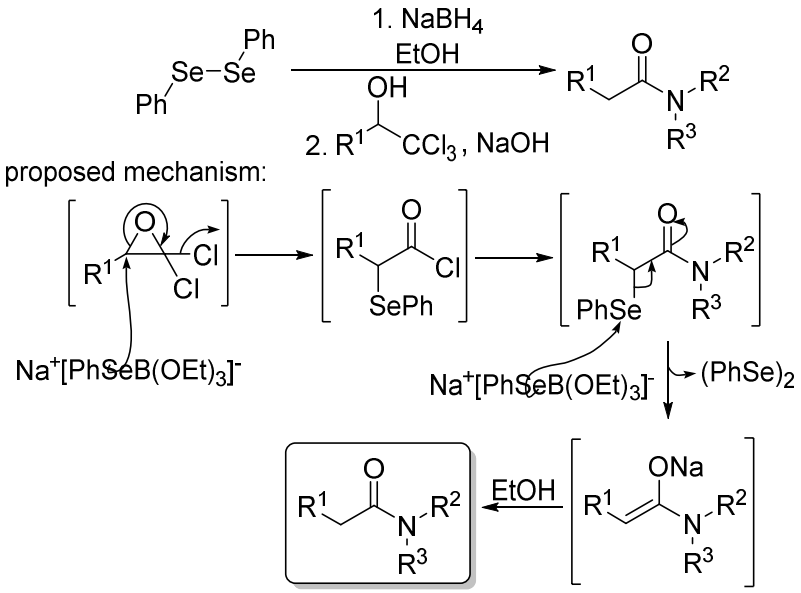
2.1.8 Jocic-type Reactions with Selenium Nucleophiles.

Due to the ever-increasing importance for one-carbon homologation-functionalisations of carbonyl compounds,[96] Snowden and coworkers developed a method involving a Jocic-type reaction with a selenium nucleophile.[93, 95]



Scheme 95 Jocic-type reaction with a selenium nucleophile.

More recently the same authors extended this methodology by trapping the acid chloride intermediate with an amine to form an amide. The mechanism for this transformation is shown in Scheme 96.



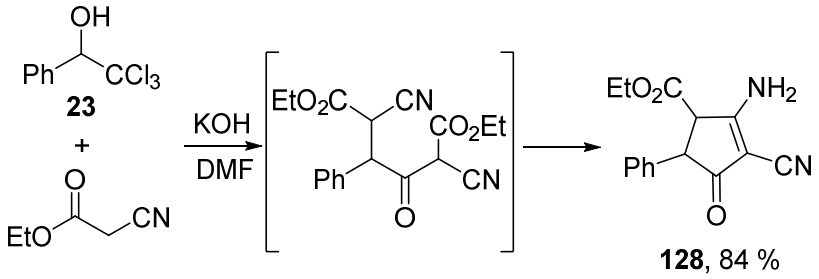
Scheme 96 One-carbon homologations *via* a Jocic-type reaction with a selenium nucleophile.

Ring-opening of the 2,2-dichloroepoxide intermediate with the phenylseleno(triethyl)-borate complex, 'PhSe^{-}', gives the acid chloride species, which is trapped with the amine nucleophile to form the α-phenylselenoamide (Scheme 96).[95] Dephenylselenation of this intermediate followed by rapid protonation leads to the desired one-carbon homologated amide (Scheme 96).[95]

Stereoselective Jocic-type reactions are not possible to study with 'PhSe-' as there is loss of the stereocentre during the reaction. In a related manner, the use of carbon nucleophiles in racemic Jocic-type reactions is limited and there is just one example of a stereospecific version (**2.1.9**).[19, 97-99]

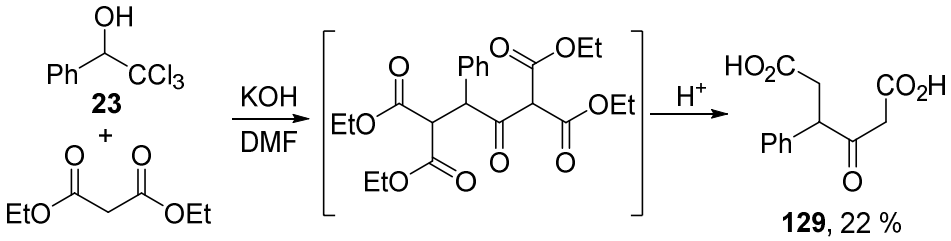
2.1.9 Jocic-type Reactions with Carbon Nucleophiles.

In 1988, Gukasyan and coworkers showed that ethyl 2-cyanoacetate could be used as a carbon nucleophile in a Jocic-type reaction for the formation of an α,β-unsaturated 5-membered ring **128** in good yield (Scheme 97).[99]



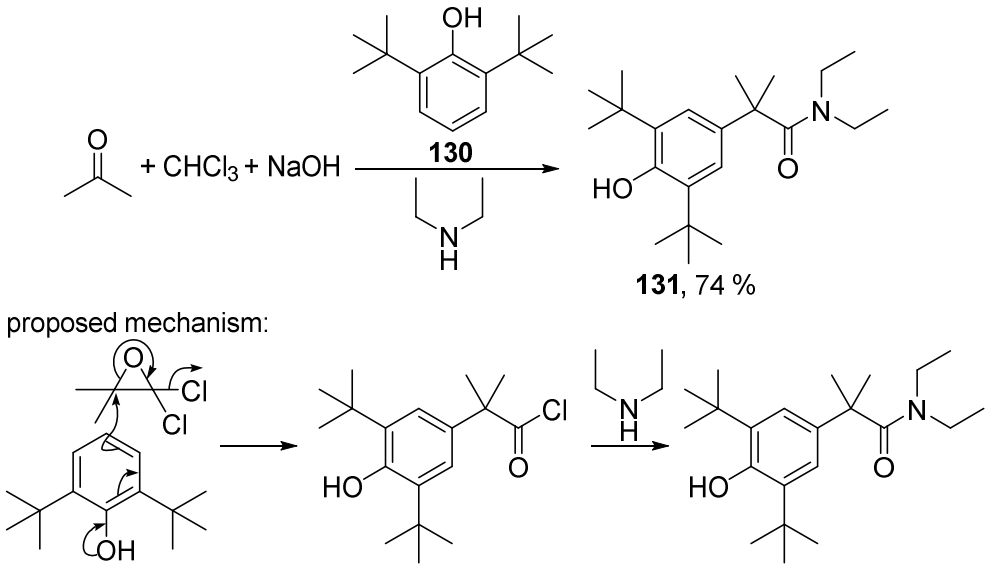
Scheme 97 First report of a carbon nucleophile in a Jocic-type reaction.

Shortly after, the same authors reported that diethyl malonate could also be used as a carbon nucleophile in a Jocic-type reaction.[97] Deprotonation of diethyl malonate leads to the carbanion which can ring-open the 2,2-dichloroepoxide with another equivalent trapping the acid chloride to ultimately form a di-acid **129** albeit in low yield (Scheme 98).



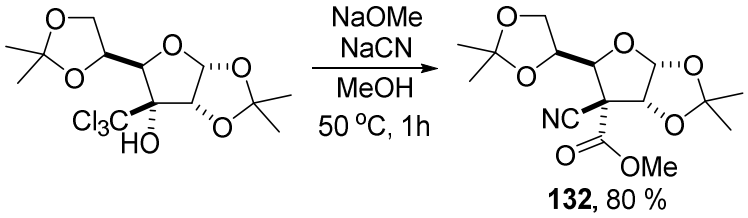
Scheme 98 Use of a carbon nucleophile in a racemic Jocic-type reaction.

In 2001, Lai reported that a hindered, activated arene, 2,6-di-*tert*-butylphenol **130**, could be used as a carbon nucleophile in a Jocic-type reaction using the 'one-pot' method starting from ketones.[16, 98] The amine in the reaction mixture traps the acid chloride intermediate to form the corresponding 2,6,-di-*tert*-butyl-4-(1,1-dialkyl-1-acetamide)-phenol **131** (Scheme 99).



Scheme 99 Use of a hindered phenol as a carbon nucleophile in a Jocic-type reaction.

In 2006, Scaffidi and coworkers discovered that sodium cyanide could be used in a stereospecific Jocic-type reaction with the product **132** being isolated with clean inversion (Scheme 100).[19]



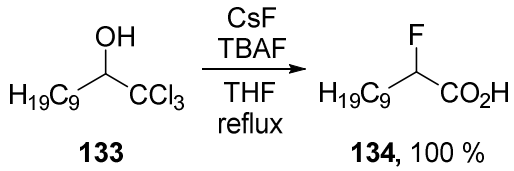
Scheme 100 Stereospecific Jocic-type reaction with the cyano moiety.

Despite the excellent yield and stereocontrol of this transformation, the scope of the cyanide moiety as a nucleophile in Jocic-type reactions is, to-date, unexplored. Another nucleophile that has been explored for both racemic and stereospecific Jocic-type reactions is fluoride (**2.1.10**).

2.1.10 Jocic-type Reactions with Fluorine as a Nucleophile.

The introduction of fluorine, especially enantioselectively, into pharmaceutical compounds is extremely important.[100, 101] Due to the diverse functional group manipulations of carboxylic acids, α-fluoro acids are ideal building blocks.[102-104]

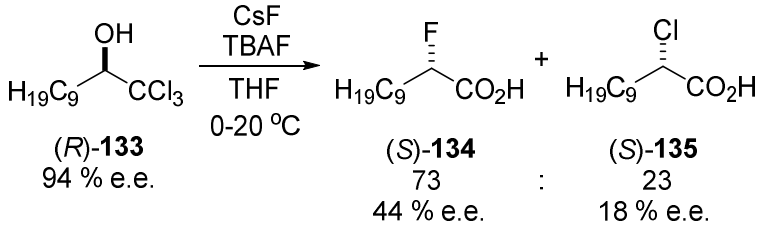
In 1994, Oliver and coworkers developed a generic method for the synthesis of these compounds using a source of fluoride in a racemic Jocic-type reaction as shown with the conversion of **133** to **134** (Scheme 101).[105]



133 **134**, 100 %

Scheme 101 Synthesis of some α-fluoro carboxylic acids *via* a Jocic-type reaction.

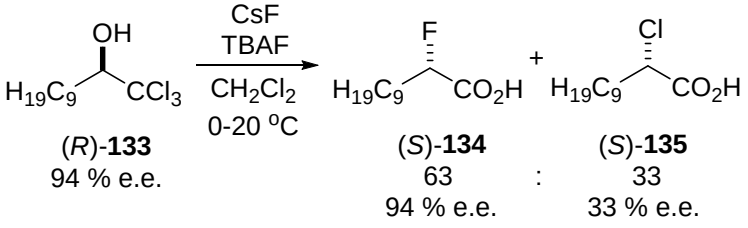
Throughout their investigations the authors noticed that at room temperature the corresponding α-chloro acid was formed as a by-product.[105] This problem was overcome by heating the reaction mixture to reflux, which eliminated all α-chloro product.[105] Shortly after, attempts from the same researchers to use these conditions with enantiomerically enriched trichlorocarbinols gave a mixture of α-fluoro and chloro acids, (*S*)-**134** and **135** respectively, in poor enantiomeric excesses (Scheme 102).[105, 106]



(*R*)-**133** 94 % e.e. (*S*)-**134** 73 : 44 % e.e. (*S*)-**135** 23 : 18 % e.e.

Scheme 102 Stereospecific Jocic-type reaction with CsF and TBAF in THF.

Modification of the reactions conditions led to significant changes in product radios as well as the enantiomeric excess of the desired α-fluoro acid (*S*)-**134.**[106] The best conditions involved using dichloromethane as the solvent (Scheme 103).

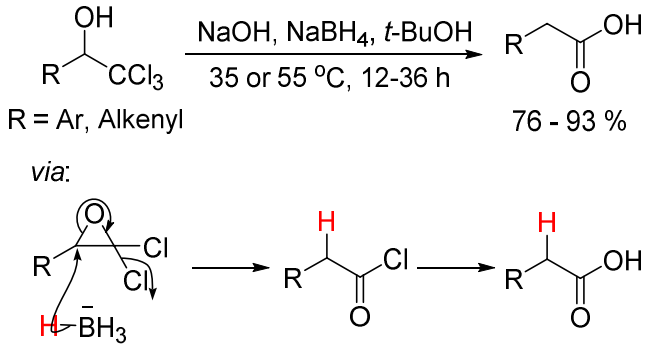


(*R*)-**133** 94 % e.e. (*S*)-**134** 63 : 94 % e.e. (*S*)-**135** 33 : 33 % e.e.

Scheme 103 Stereospecific Jocic-type reaction with fluorine in dichloromethane.

2.1.11 Jocic-type Reactions with Hydrogen as a Nucleophile.

Snowden and coworkers showed that 'H^-', in the form of sodium borohydride, could be used a Jocic-type reaction (Scheme 104).[93]



Scheme 104 Sodium borohydride used in a Jocic-type reaction.

The same authors showed that deuterated sodium borohydride could be used to give the corresponding α-monodeuterated acid, which can easily be converted carboxylic acid derivatives such as ketones or alcohols.[93]

As described in section **2.2**, there has been a significant amount of work reported regarding Jocic-type reactions, including elucidation of the mechanism and the exploration of the different types of nucleophiles that can be exploited. With this in mind we wanted to further investigate some stereospecific Jocic-type reactions.

2.2 RESEARCH AIMS

Initially, the scope of Jocic-type reactions with amine nucleophiles using enantiomerically enriched trichlorocarbinols was to be explored. This is because of the potential use of the products as pharmaceutical building blocks and the surprising lack of stereoselective Jocic-type reactions using amine nucleophiles in the literature. Furthermore, we wanted to explore the use of bis-amine nucleophiles in reactions for the synthesis of medicinally relevant cyclic amino-amides, such as piperazin-2-ones,[107]

diazepan-2-ones[108-110] and 3,4-dihydroquinoxalin-2(1*H*)-ones.[111] A few of the common syntheses for this class of compounds are discussed in section **2.3.1**.

2.2.1 Synthesis of Enantiopure Piperazin-2-ones and Related Compounds.

Substituted piperazin-2-ones, and related piperazines, are important pharmacophores[107, 111-113] which can be found in several medicinally relevant compounds (Figure 39).[109, 114-153]

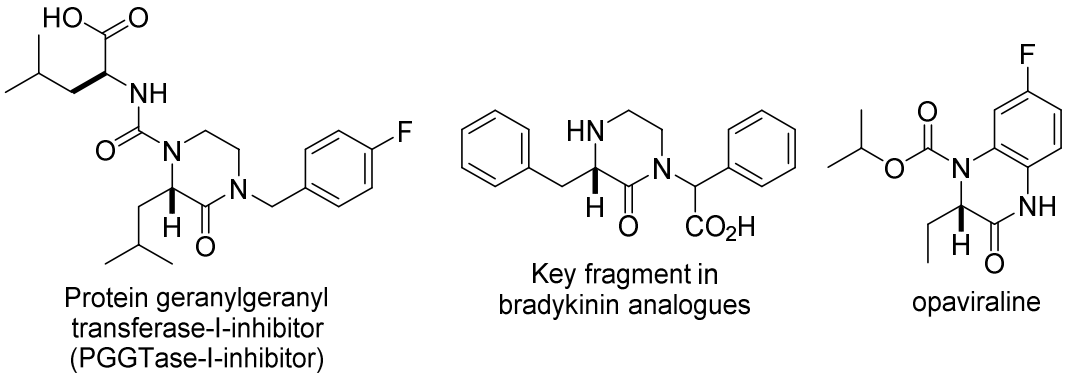
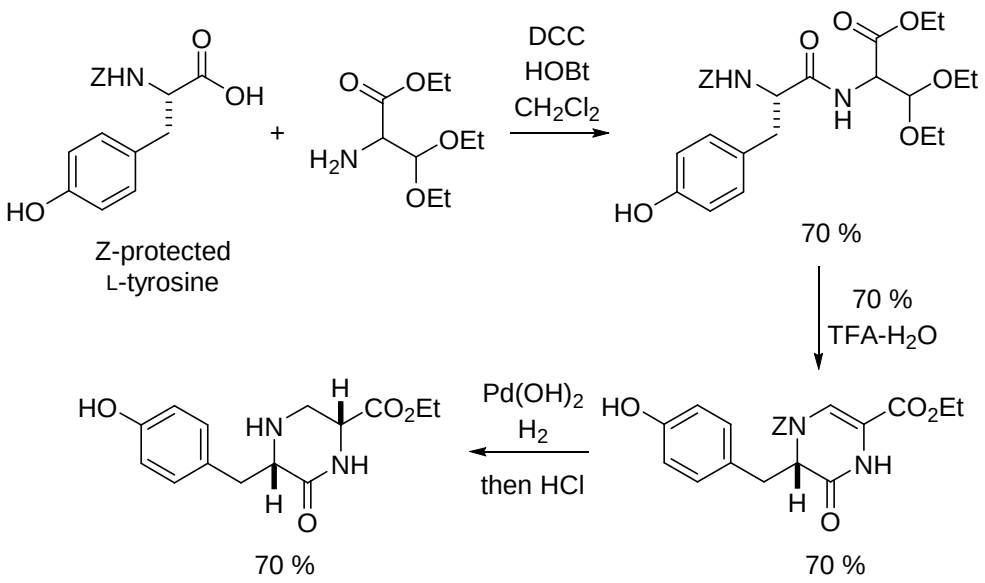


Figure 39 Some medicinally relevant compounds containing an enantiomerically enriched piperazin-2-one core.

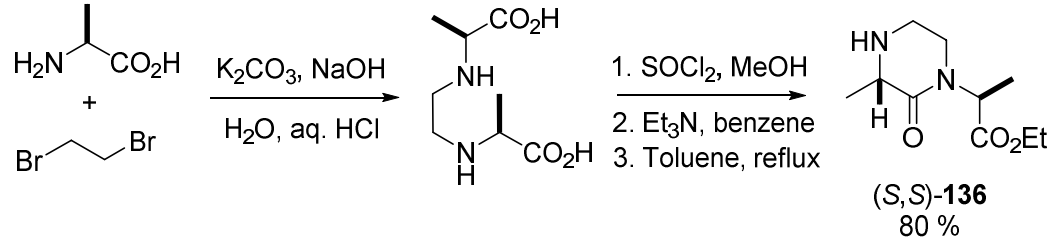
While the synthesis of 1- and 4-substituted piperazin-2-ones has been reported in the literature, the synthesis of enantiomerically enriched versions remain a great challenge.[113, 120, 128, 129, 154, 155] To date, substituted piperazin-2-ones can be made stereoselectively from the manipulation of 'chiral pool' compounds such as α-amino acids,[112, 120, 153, 154, 156] the dynamic resolution of α-halo chiral esters[113, 157] and the kinetic resolution of *N*-heterocycles.[158]

In 1989, DiMaio and Belleau used L-tyrosine-derived for the synthesis of enantiomerically enriched piperazin-2-ones *via* the stereospecific reduction of an enamide (Scheme 105).[153]



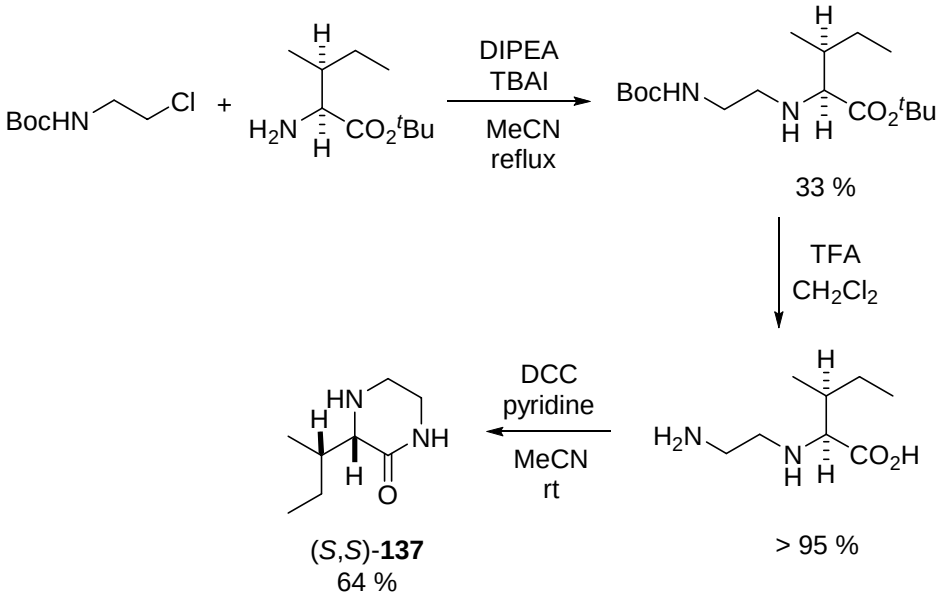
Scheme 105 Synthesis of L-tyrosine-derived enantiomerically enriched piperazin-2-ones.

Ohsuka and coworkers showed that an enantiomerically enriched 1-substituted piperazin-2-one (*S*,*S*)-**136** could be prepared from L-alanine *via* a double addition to 1,2-dibromoethane and subsequent ring closure (Scheme 106).[112, 159]



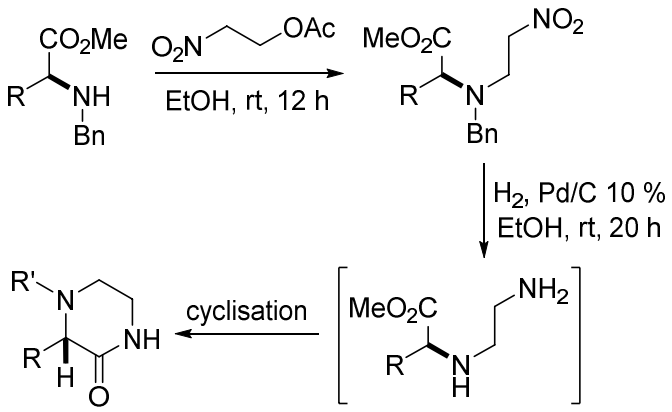
Scheme 106 Synthesis of enantiomerically enriched 1-substituted piperazin-2-ones from L-alanine.

Bryce and coworkers also used this method for the preparation of related analogues starting from L-phenylalanine and L-tryptophan.[160] Other popular methods for the synthesis of enantiomerically enriched piperazin-2-ones using chiral α-amino acid precursors include those reported by Schofield[120] and Zanirato.[154] A series of elastase inhibitors bearing piperazin-2-one rings were synthesised by Schofield and coworkers in 2003.[120] Many α-amino acid derived products, such as (*S*,*S*)-**137**, were reported such as those from L-isoleucine *tert*-butyl ester (Scheme 107).[120]



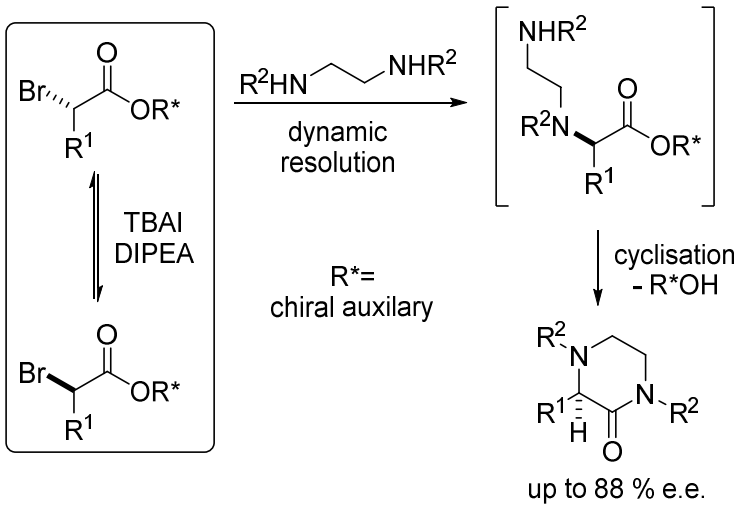
Scheme 107 Synthesis of enantiomerically enriched piperazin-2-ones from L-isoleucine *tert*-butyl ester.

Shortly after, Zanirato and coworkers reported a generic method for the synthesis of 4-substituted enantiopure piperazin-2-ones (Scheme 108).[154] The starting α-amino acid esters were reacted with 2-acetyloxy-1-nitroethane, a stable precursor for nitroethylene, to give the expected Michael adducts.[154] Subsequent hydrogenation led to the formation of piperazin-2-ones *via* the amine intermediate (Scheme 108).



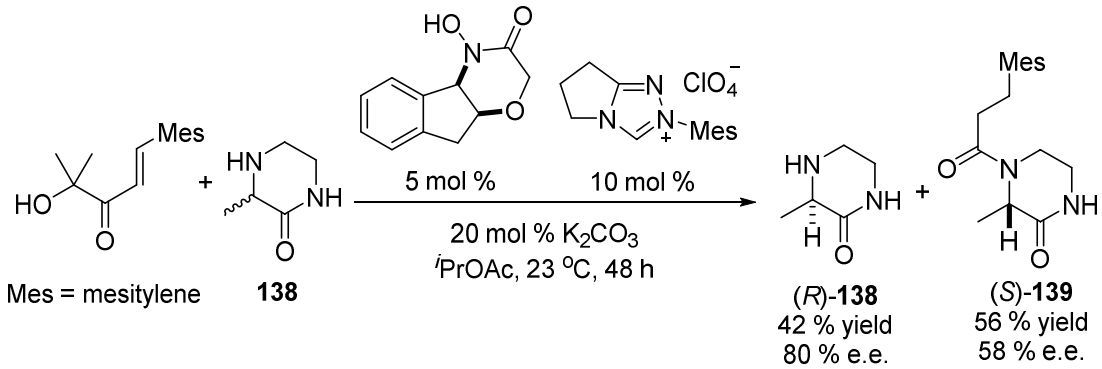
Scheme 108 Synthesis of enantiopure 4-substituted piperazin-2-ones *via* a Michael addition.

Another method for the synthesis of enantiomerically enriched piperazin-2-ones includes the dynamic resolution of α-halo esters as shown by Jang and coworkers in 2011 (Scheme 109).[113]



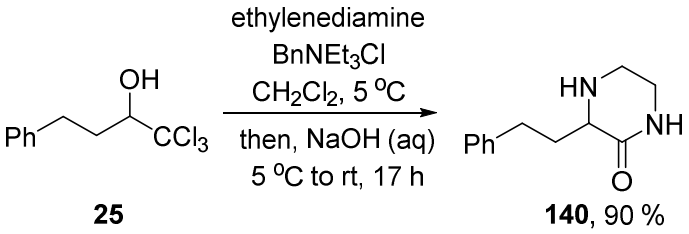
Scheme 109 Dynamic resolution of α-halo esters for the synthesis of enantiomerically enriched piperazin-2-ones.

More recently, Bode and coworkers showed that *N*-heterocyles, such as 3-methylpiperazin-2-one **138**, can be kinetically resolved to give enantiomerically enriched amines and their corresponding enantiomerically enriched amides, (*R*)-**138** and (*S*)-**139** in this case (Scheme 110).[161, 162]



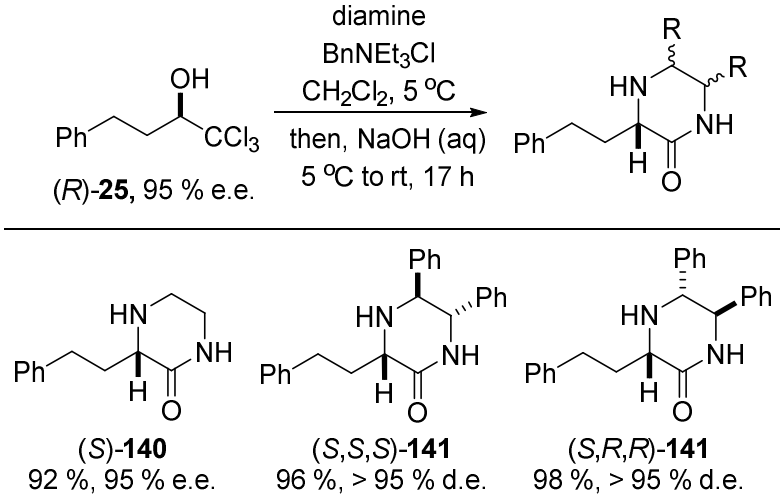
Scheme 110 Chiral hydroxamic acid-catalysed kinetic resolution of (±)-3-methylpiperazin-2-one.

Many of the procedures described in this section are reliant on reactions with chiral α-amino acids. With a view to develop a generic method for the synthesis of these classes of compounds, Matthew Harris, during his PhD in the Fox group, showed that it was possible to synthesise racemic piperazin-2-one **140** in an excellent yield (Scheme 111).[163, 164]



Scheme 111 Previously reported work in the Fox group.

Also, following the development of the general method for the synthesis of enantiomerically enriched trichlorocarbinols (Chapter 1), Harris went on to show that stereospecific versions were possible from (*R*)-**25** (Scheme 112).[163, 164]



Scheme 112 Stereospecific Jocic-type reaction with diamine nucleophiles by Harris.

Following this we wanted to widen the scope of this reaction in order to add to the literature a general method for the synthesis of enantiomerically enriched amino-amides as well as piperazin-2-ones and related compounds. The development of this work is discussed in section **2.4**.

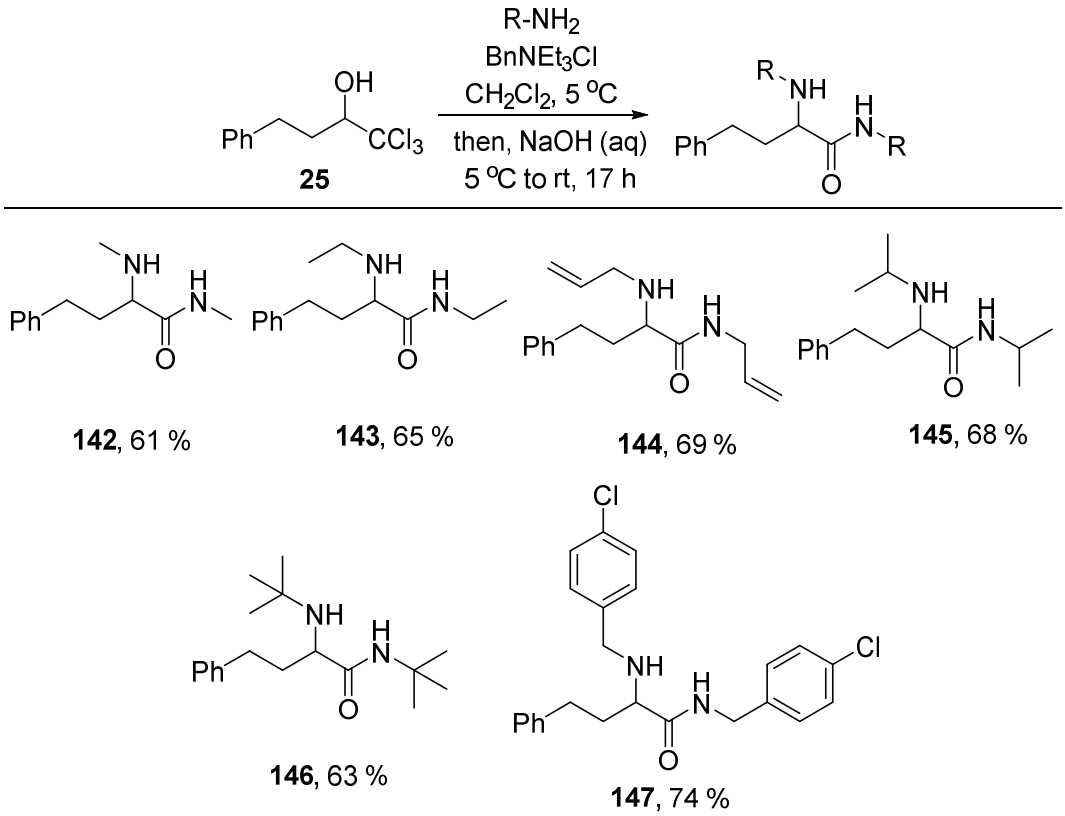
2.4 RESULTS AND DISCUSSION

2.4.1 Synthesis of Amino-amides.

Before we could explore the use of mono- and bis-amine nucleophiles in Jocic-type reactions with enantiomerically enriched trichlorocarbinols we first required to find

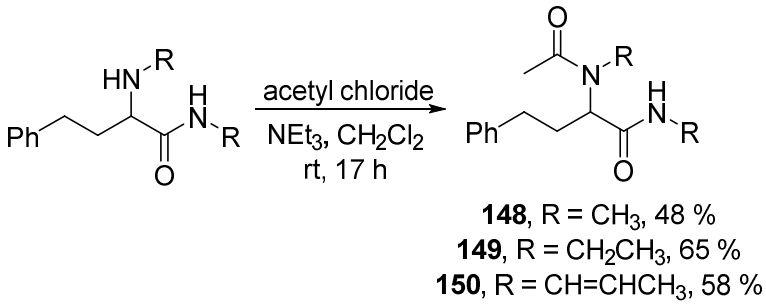
suitable conditions and also to ensure that we could split the products using chiral HPLC.

Using modified conditions from those reported by Lai in 1980,[6] we were able to synthesise a variety of racemic amino-amides (**142**-**147**) in good yield (Scheme 113).[164]



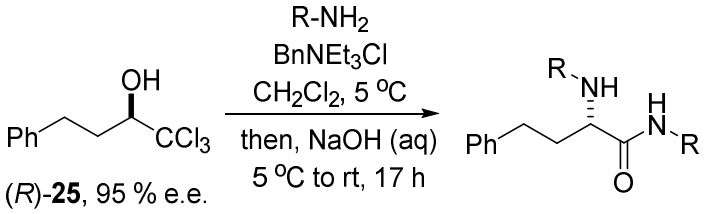
Scheme 113 Racemic Jocic-type reactions with 2,2,2-trichloro-4-phenylbutan-2-ol and amine nucleophiles.

Racemic amino-amides **145**-**147** were resolved by chiral HPLC, however in order to fully resolve **142**-**144** the corresponding *N*-acyl derivatives were required to be synthesised (Scheme 114).



Scheme 114 Synthesis of *N*-acyl derivatives of racemic amino-amides **148**-**150**.

Following this, stereospecific Jocic-type reactions using the same amines and conditions as described in Scheme 113 were attempted with (*R*)-2,2,2-trichloro-4-phenylbutan-2-ol, (*R*)-**25**, which was synthesised from the asymmetric transfer hydrogenation of 2,2,2-trichloro-4-phenylbutan-2-one **54** (see Chapter 1). The products were isolated in good yields and excellent enantiomeric excesses (Table 7).



Entry	R	Yield (%)	e.e.	Config.	Product
1	CH_3	65	92[a]	*S*[c]	**142**
2	CH_2CH_3	69	95[a]	*S*[c]	**143**
3	$CH_2CH{=}CH_2$	70	97[a]	*S*[d]	**144**
4	$CH_2(CH_3)_2$	69	97[b]	*S*[c]	**145**
5	$C(CH_3)_3$	59	95[b]	*S*[c]	**146**
6	4-$ClC_6H_5CH_2$	66	93[b]	*S*[d]	**147**

[a] HPLC analysis on *N*-acetyl derivative. [b] HPLC analysis. [c] by analogy with (*S*)-**144** and (*S*)-**147**. [d] X-ray crystallography.

Table 7 Jocic-type reactions with mono-amine nucleophiles and (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol.

The absolute stereochemistry of the hydrochloride salt of amino-amide (*S*)-**144**, (*S*)-**144**.HCl, and (*S*)-**147** were established by X-ray crystallography (Figure 40). The observed (*S*)-stereochemistry is consistent with the inversion of stereochemistry observed in related Jocic reactions.[16]

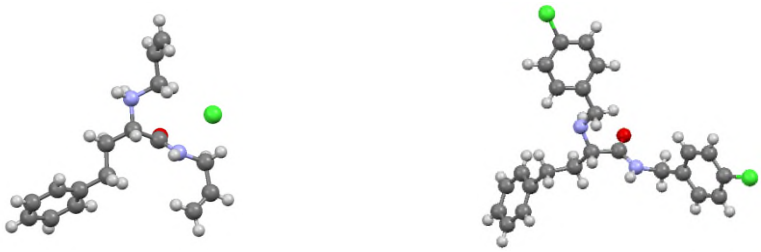
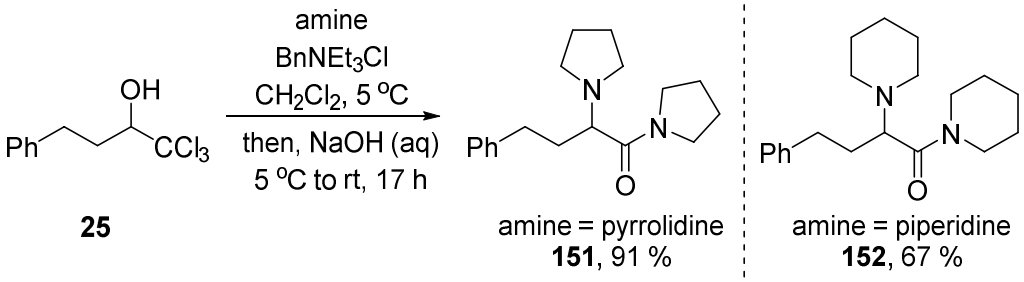


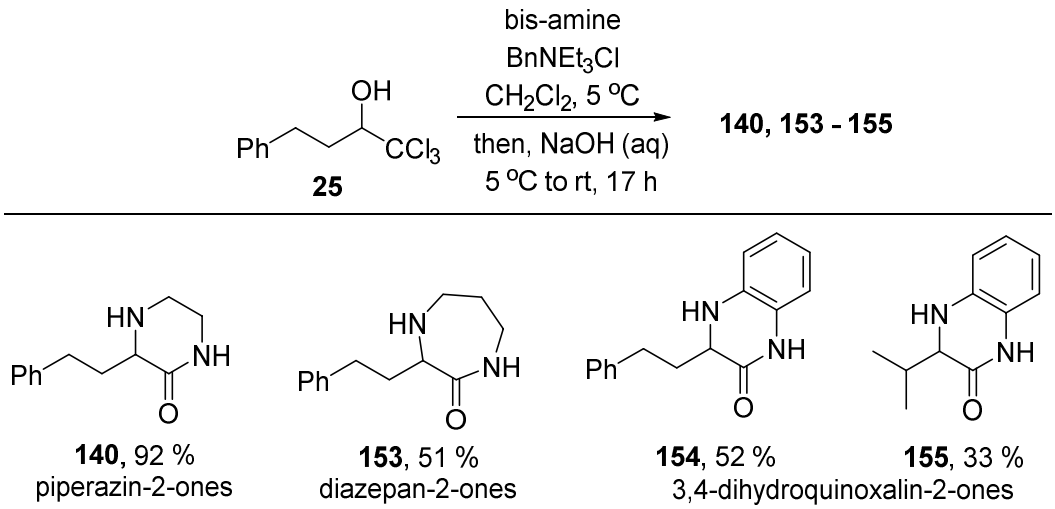
Figure 40 X-ray crystal structures of (*S*)-**144**.HCl and (*S*)-**147**.

With a view to extend the scope of the amine in this reaction, we showed that secondary amines were excellent nucleophiles with the preparation of amino-amides **151** and **152**, both of which were split using chiral HPLC (Scheme 115).



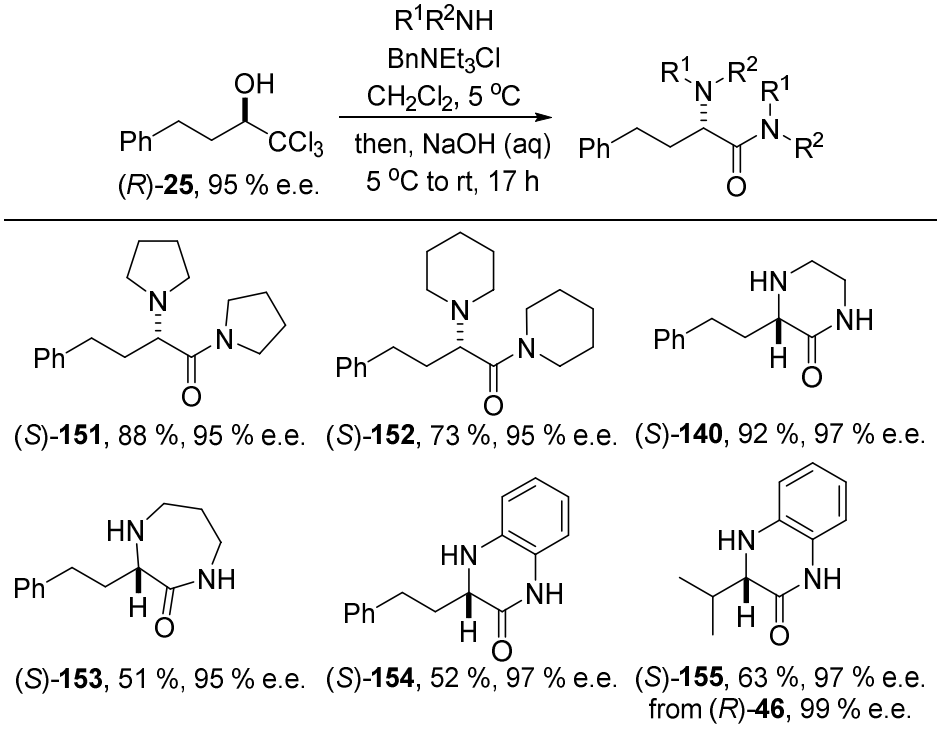
Scheme 115 Racemic Jocic-type reaction with secondary amines pyrrolidine and piperidine.

Since we were interested in synthesising piperazin-2-ones, diazepan-2-ones and 3,4-dihydroquinoxalin-2-ones (see section **2.3**), we attempted Jocic-type reactions with the relevant bis-amine nucleophiles. Racemic versions were prepared from the reaction of 2,2,2-trichloro-4-phenylbutan-2-ol **25** with 1,3-diaminopropane, *o*-phenylenediamine or as previously shown with ethylenediamine (Scheme 116).[163] Compound **155** was synthesised from 1,1,1-trichloro-4-methylpentan-2-ol **46** since it has previously been reported enantiomerically enriched and thus comparison of the sign of the rotation for stereochemistry assignment was possibe for the assignment of absolute configuration of this compound.[165]



Scheme 116 Synthesis of racemic piperazin-2ones, diazepan-2-ones and 3,4-dihydroquinoxalin-2-ones *via* Jocic-type reactions with bis-amine nucleophiles.

Following the successful synthesis, and resolution by chiral HPLC, of **140** and **151**-**155** stereoselective versions were prepared in good yield and exellent enantiomeric excesses (Scheme 117).



Scheme 117 Stereoselective Jocic-type reactions with secondary and bis-amines.

The stereochemistry of (*S*)-**155** was the same as the compound synthesised from L-valine.[165] As shown in section **2.3** the majority of the medicinally relevant piperazin-2-

ones are substituted at either the 1- or 4-position, which is shown with PGGTase-I inhibitors in Figure 41.[122]

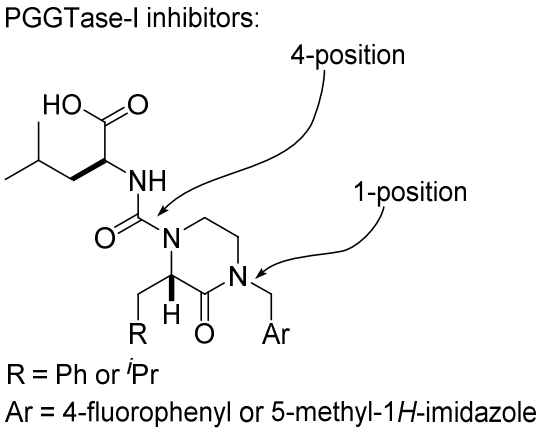
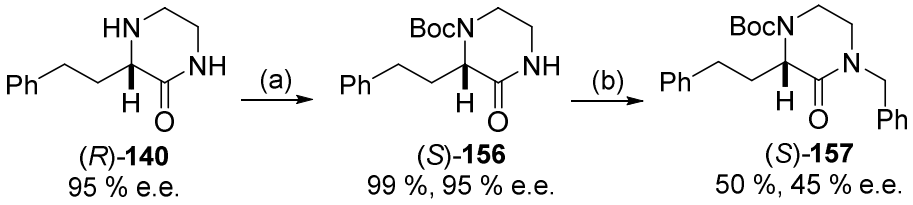


Figure 41 Substituted piperazin-2-ones with 1- and 4-labelling shown.

Following the successful development of a generic method for unsubstituted piperazin-2-ones and related compounds we decided to focus our efforts on the preparation of substituted versions as shown in **2.4.2**.

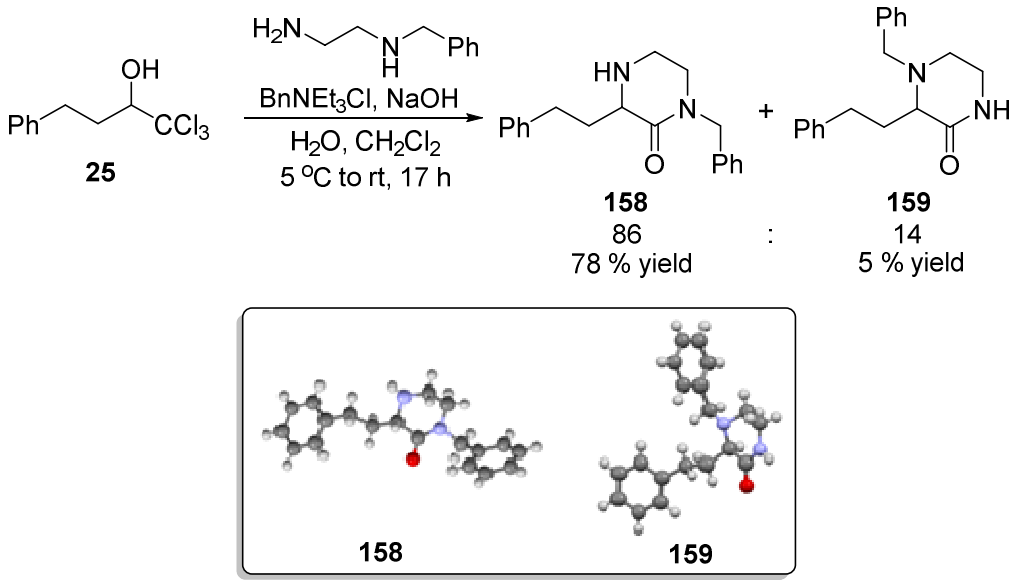
2.4.2 Synthesis of Substituted Piperazin-2-one (*S*)-140, Diazepan-2-one (*S*)-153 and 1,4-Quinoxalin-2-one (*S*)-154.

We began with attempts to synthesise (*S*)-1-benzyl-3-phenethylpiperazin-2-one (*S*)-**158** from (*S*)-**140**. In order to alkylate the amido-nitrogen protection of the amino-site was required. Boc-protection of (*S*)-**140** gave (*S*)-**156** in excellent yield and without loss of stereochemical integrity (Scheme 118). However, deprotonation of the amido-NH with sodium hydride and subsequent alkylation with benzyl bromide led to the formation of the product (*S*)-**157** in 45 % e.e., which is a loss of 40 % e.e.



Scheme 118 *N*-alkylation of Boc-protected piperazin-2-ones. Reagents and conditions: (a) Boc_2O, NaOH, H_2O, THF, rt, 17 h; (b) NaH, THF, 0 °C, 90 min.; then BnBr, 0 °C to rt, 18 h.

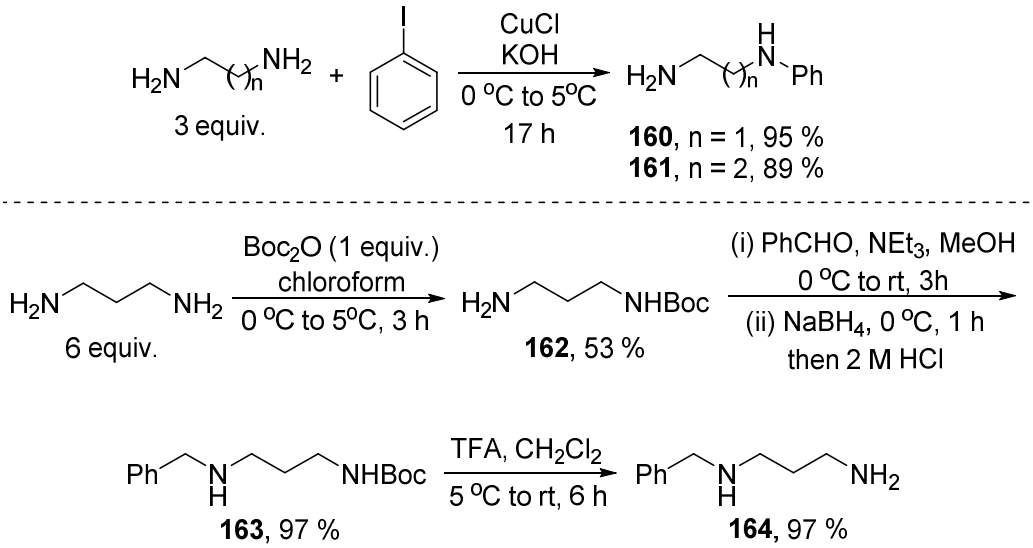
Thus, it became apparent that it was not possible to synthesise 1-substituted analogues in this way without loss of stereochemical integrity. In an attempt to develop an alternative method for the preparation of 1-substituted piperazin-2-ones, the regioselectivity of Jocic-type reactions with unsymmetrical diamines was investigated. Matthew Earl, a summer student in the Fox group, showed that the reaction with *N*-benzylethylenediamine gave a mixture of products but a strong preference for the 1-substituted analogue (Scheme 119).[166] The regiochemistry of the products was confirmed from X-ray crystallography.[166]



Scheme 119 Jocic-type reaction with *N*-benzylethylenediamine with X-ray crystal structures.

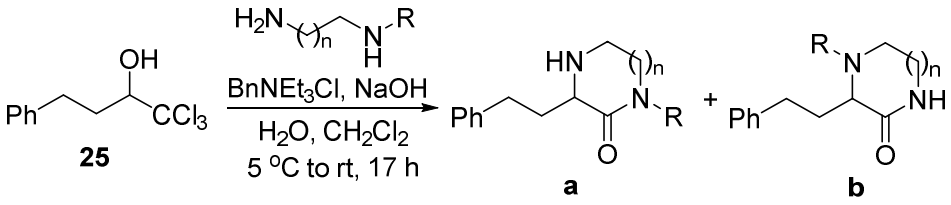
Not only was **158** preferentially formed in a good ratio (86 : 14) the products were easily separated using silica column chromatography, since they are chemically very different, giving the major regio-isomer **158** in a good 78 % yield (Scheme 119). Following this promising result we investigated Jocic-type reactions with commercially available *N*-methyl, -ethyl and -isopropyl ethyleneidiamines (Table 8, entries 2-4). In order to broaden the scope of the substrates we synthesised *N*-phenylethylenediamine

160, *N*-phenylpropane-1,3-diamine **161** and *N*-benzylpropane-1,3-diamine **164** (Scheme 120).[167, 168]



Scheme 120 Synthesis of *N*-phenylethylenediamine and *N*-phenylpropane-1,3-diamine.

Table 8 shows the product ratios and isolated yields for the Jocic-type reactions with 2,2,2-trichloro-4-phenylbutan-2-ol **25** and unsymmetrical diamines.



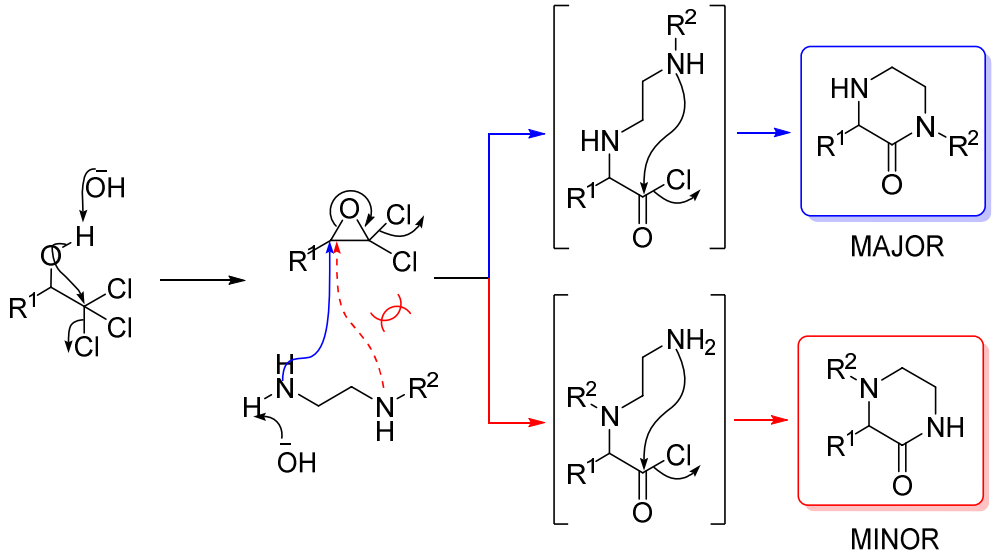
Entry	R	n	Ratio[a]	Yield[b]			
			a : b	a	b	a	b
1	CH_2Ph	1	86 : 14	78	5	**158**	**159**
2	CH_3	1	50 : 50	47	41	**165**	**166**
3	CH_2CH_3	1	75 : 25	72	8	**167**	**168**
4	$CH_2(CH_3)_2$	1	95 : 5	64	2	**169**	**170**
5	Ph	1	> 90 : 10	51	-[c]	**171**	-[c]
6	CH_2Ph	2	73 : 27	48	9	**172**	**173**

[a] by ^{1}H NMR. [b] isolated yield. [c] not isolated.

Table 8 Racemic Jocic-type reactions with unsymmetrical diamines.

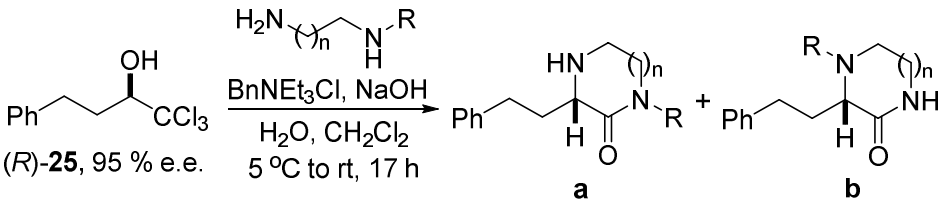
As the size of the R group on the di-amine increases the formation of 1-substituted piperazin-2-ones is favoured. When R = methyl (entry 2) there is no preference for

either the 1- or 4-substituted piperazin-2-one, giving an equal mixture of **165** and **166**. However, increasing the size of R to ethyl gives a much improved ratio of 75 : 25 (entry 3), which increases further with isopropyl to 95 : 5 (entry 4). We also showed that this reaction worked well with *N*-phenylethylenediamine, which gives almost exclusive 1-substituted product **171** (entry 5) and also with *N*-benzyl-1,3-propanediamine for the synthesis of substituted 7-membered diazepam-2-ones (entry 6). The formation of the 1-substituted piperazin-2-one may be favoured by the preferential attack of the less sterically encumbered primary amine opening the 2,2-dichloroepoxide (Scheme 121).



Scheme 121 Proposed mechanism for the preferential formation of 1-substituted piperazin-2-ones over 4-substituted piperazin-2-ones.

Following the successful isolation and characterisation all of the products, or derivatives, were split using chiral HPLC. Stereospecific Jocic-type reactions with (*R*)-2,2,2-trichloro-4-phenylbutan-2-ol (*R*)-**25** and the substituted diamines gave the major 1-substituted regio-isomers in good yields and enantiomeric excesses (Table 9).

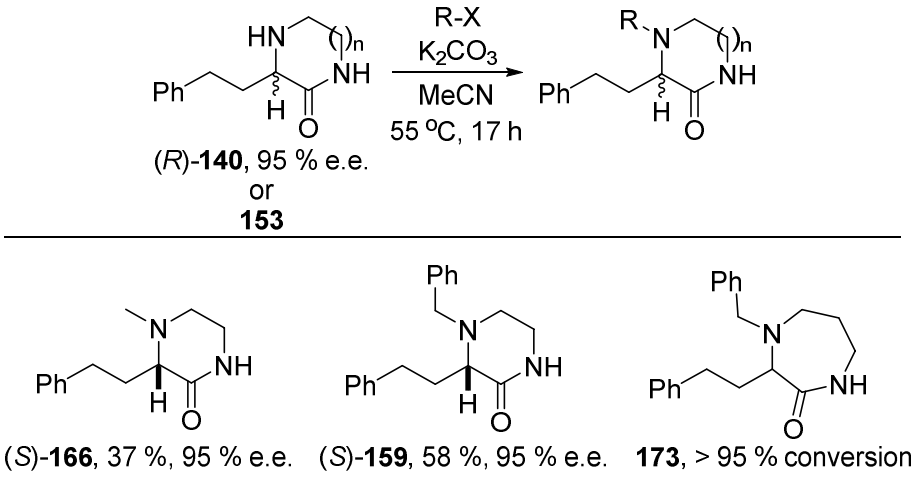


Entry	R	n	Yield[a]		e.e.[b]			
			a	b	a	b	a	b
1	CH_2Ph	1	76	6	95[c]	98	**(*S*)-158**	**(*S*)-159**
2	CH_3	1	46	41	94	96	**(*S*)-165**	**(*S*)-166**
3	CH_2CH_3	1	72	5	96	95	**(*S*)-167**	**(*S*)-168**
4	$CH_2(CH_3)_2$	1	72	-	99	-	**(*S*)-169**	-
5	Ph	1	52	-	98	-	**(*S*)-171**	-
6	CH_2Ph	2	53	11	99	97	**(*S*)-172**	**(*S*)-173**

a isolated yield. b by HPLC. c by HPLC of *N*-Boc derivative.

Table 9 Stereospecific Jocic-type reactions with unsymmetrical diamines.

Despite the much lower yields for the minor 4-substituted regio-isomers the enantiomeric excesses were still excellent. With a view to develop a general method for the synthesis of 4-substituted piperazin-2-ones and diazepan-2-ones we reacted unsubstituted (*S*)-3-phenethylpiperazin-2-one (*S*)-**140** and 3-phenethyl-1,4-diazepan-2-one **153** with the corresponding alkylating agent and potassium carbonate in acetonitrile at 55 °C (Scheme 122).



Scheme 122 Alkylation of piperazin-2-one (*S*)-**140** and diazepan-2-one **153**.

The alkylated products (*S*)-**159** and (*S*)-**166** were isolated in moderate yields and maintained excellent enantiomeric excesses. We are confident that the minor regio-isomers (Table 9) are the 4-substituted products since the ^{1}H NMR spectra of those obtained by alkylations (Scheme 122) were identical. Furthermore, an X-ray crystal structure of **171** provided additional evidence for the regiochemistry assignment. (Figure 42).

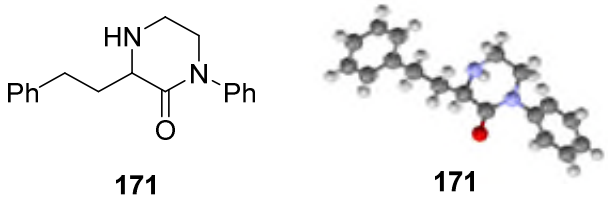
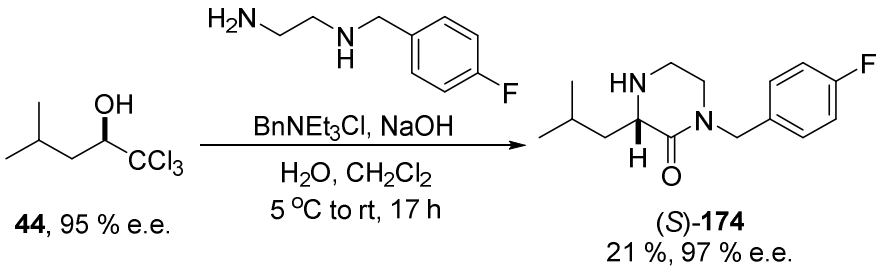


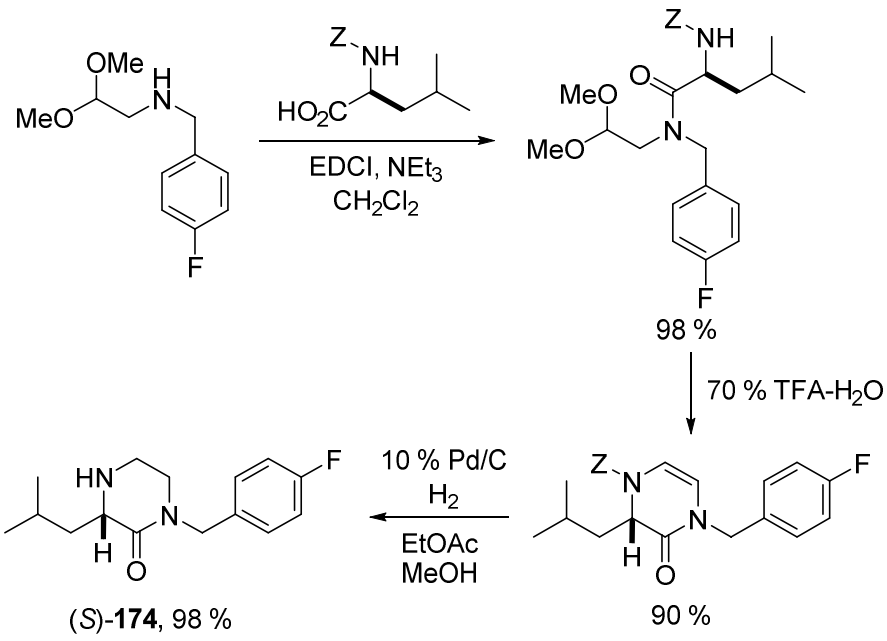
Figure 42 X-ray crystal structure of **171**.

In order to demonstrate the utility of this method, a key intermediate in the synthesis of PGGTase-I inhibitor (*S*)-**174**[122] was completed in excellent enantiomeric excess by Sam Greatorex, a fourth year undergraduate student in the Fox group.[169]



Scheme 123 Synthesis of PGGTase-I inhibitor (*S*)-**174**.

This method offers advantages over the reported synthesis for analogues of these compounds.[122] The main disadvantage of the route shown in Scheme 124 is that analogues bearing naturally occurring or otherwise available α-amino acids could only be synthesised. The method shown in Scheme 123 allows the preparation of a wider variety of substrates, providing the enantiopure trichlorocarbinol can be syntheised from the asymmetric hydrogenation of the corresponding ketone.



Scheme 124 Previously reported synthesis of (*S*)-**174**.

In addition substituted piperazin-2-ones bearing an α-benzyl side chain are favoured in several medicinally important building blocks such as conformationally restricted peptidomimetics (Figure 43).[147, 152]

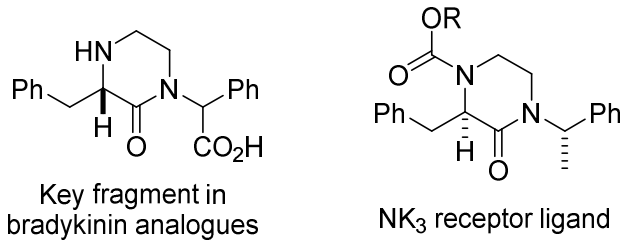
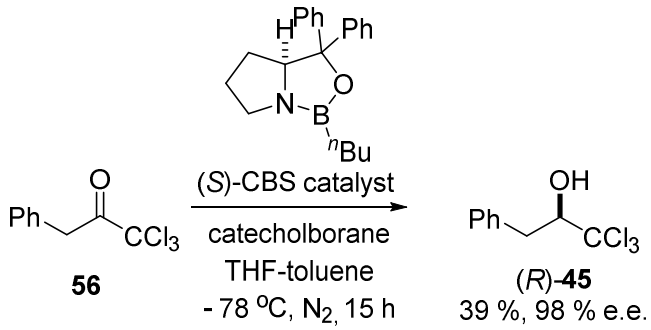


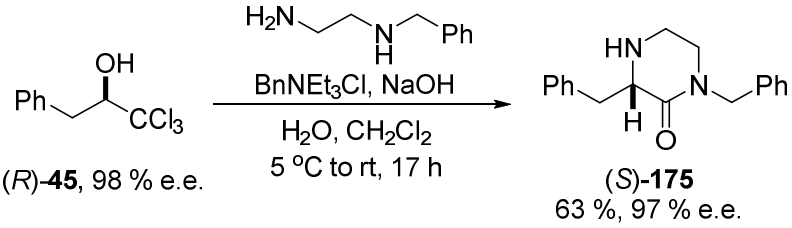
Figure 43 Medicinally relevant substituted piperazin-2-ones bearing an α-benzyl side chain.

Using asymetric transfer hydrogenation, it is not possible to synthesise enantiopure 1,1,1-trichloro-2-phenylpropan-2-ol **45** (see Chapter 1), which is the required starting material for Jocic-type reactions for the synthesis of these class of substrates. However, Sam Greatorex showed that the asymmetric reduction of 1,1,1-trichloro-3-phenylpropan-2-one **56** using the (*S*)-CBS-catalyst gives the desired corresponding alcohol (*R*)-**45** in an excellent 98 % enantiomeric excess.[169]



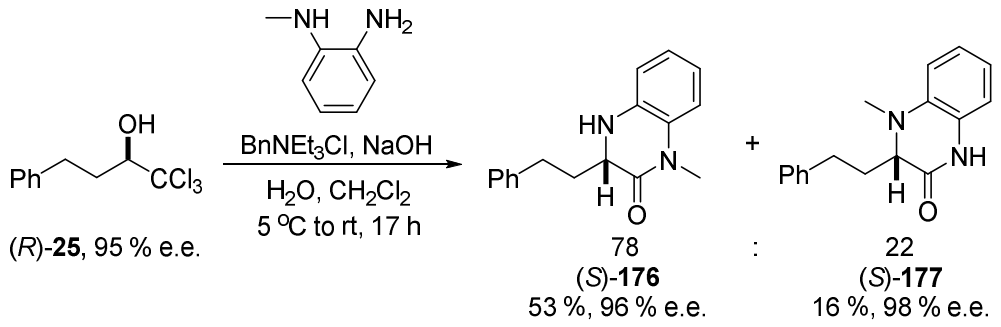
Scheme 125 Asymmetric reduction using the (*S*)-CBS-catalyst to afford (*R*)-**45**.

Using (*R*)-**45**, Sam Greatorex showed that the synthesis of compounds similar to those shown in Figure 43 is now possible *via* a Jocic-type reaction, such as the isolation of (*S*)-1,3-dibenzylpiperazin-2-one (*S*)-**175** in good yield and excellent enantiomeric excess (Scheme 125).[169]



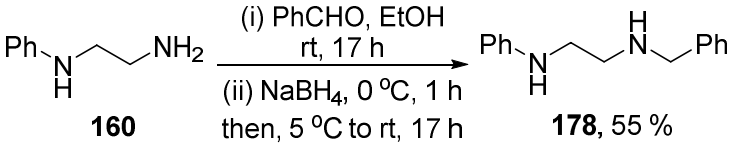
Scheme 126 Synthesis of (*S*)-**175** *via* a Jocic-type reaction with *N*-benzylethylenediamine.

The synthesis of enantiopure 1-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones are of great interest as pharmaceutical building blocks,[170-173] for example in antagonists of the *N*-methyl-D-aspartate receptor.[174, 175] As previously shown the synthesis of unsubstituted versions of these compounds are possible in good yield and excellent enantiomeric excesses (Scheme 117). The reaction of (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** with *N*-methyl-1,2-ethylenediamine in a Jocic-type reaction gives a mixture of the 1- and 4-substituted products (Scheme 127). As with the substituted piperazin-2-ones and diazepan-2-ones, these regio-isomers are separable by silica column chromatography giving the individual products (*S*)-**176** and (*S*)-**177** in excellent enantiomeric excess.



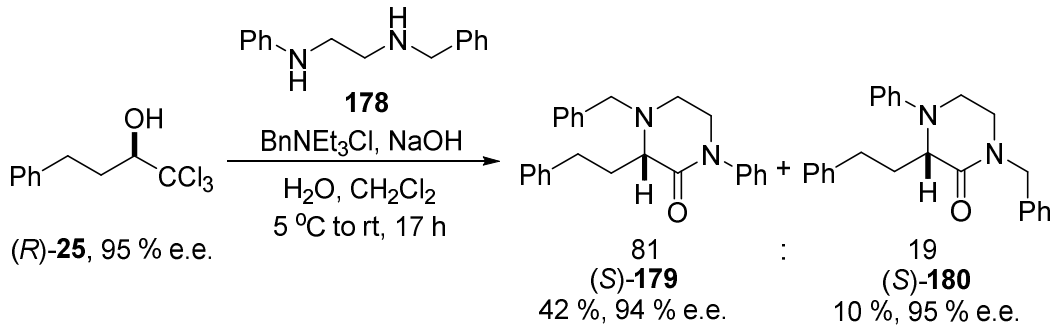
Scheme 127 Synthesis of substituted 3,4-dihydroquinoxalin-2(1*H*)-ones (*S*)-**176** and (*S*)-**177**.

Following the success of the Jocic-type reactions with monosubstituted diamines we wanted to investigate the scope further using a disubstituted diamine. In order to prepare the reactivity of *N*-phenyl and *N*-benzyl, N^1-phenyl-N^2-benzyl-ethylenediamine **178** was synthesised in good yield (Scheme 128).



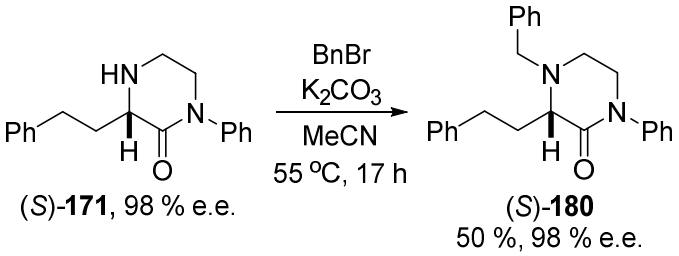
Scheme 128 Synthesis of N^1-phenyl-N^2-benzyl-ethylenediamine.

The Jocic-type reaction of (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** with N^1-phenyl-N^2-benzyl-ethylenediamine **178** gave a mixture of products with a strong preference for the 1-phenyl substituted piperazin-2-one (*S*)-**179** with a 81 : 19 ratio and also gave both regio-isomers in excellent enantiomeric excess (Scheme 129).



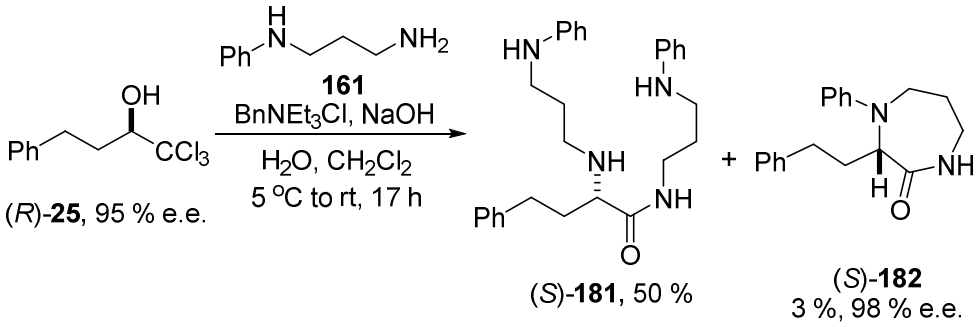
Scheme 129 Synthesis of piperazin-2-ones (*S*)-**179** and (*S*)-**180** from (*R*)-**25**.

The regio-chemistry of (*S*)-**180** was confirmed by its independant synthesis *via* the benzylation of (*S*)-**171** (Scheme 130).



Scheme 130 Independent synthesis of (*S*)-**180** for conformation of regio-chemistry.

Since the isolation of 1-benzyl-substituted diazepan-2-one (*S*)-**172** was possible in good yield and enantiomeric excess (Table 9, entry 6) we attempted the synthesis of the phenyl-substituted analogue. However, the Jocic-type reaction of (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** with *N*-phenyl-1,3-diaminopropane **161** gave the amino-amide (*S*)-**181** as the major product in 50 % yield whilst giving the cyclised 4-substituted product (*S*)-**182** in only 3 % isolated yield (Scheme 131).



Scheme 131 By-product formation from the reaction of (*R*)-**25** with **161**.

The steric hindrance and reduced nucleophilicity of the phenyl-substituted amine indicates that the intermolecular addition of a second equivalent of NH_2 of bis-amine **161** is faster than the formation of the 7-membered ring (Figure 44). However, when the phenyl-substituted amine opens the 2,2-dichloroepoxide species then the intramolecular ring closure to form the diazepan-2-one is favoured over the intermolecular attack of a second bis-amine nucleophile (Figure 44).

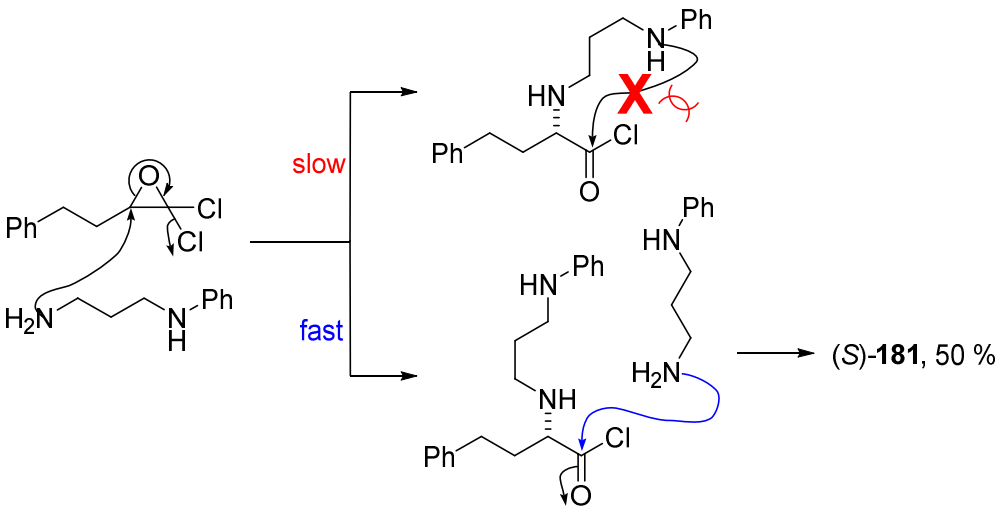
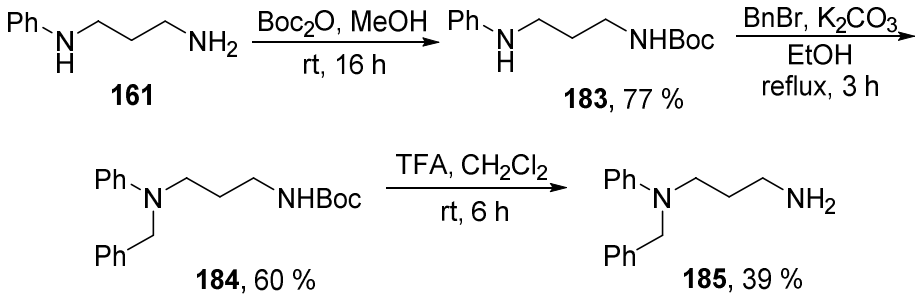


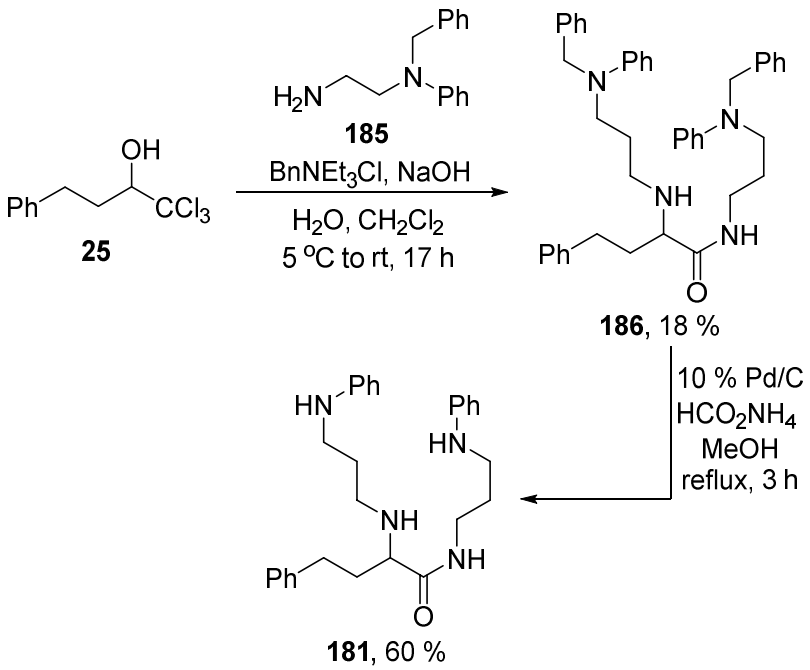
Figure 44 Proposed mechanism for the formation of products (*S*)-**181**.

In order to confirm the structure of (*S*)-**181** it had to be prepared independently. For the chosen route N^1-phenyl-N^1-benzylpropane-1,3-diamine **185** was required to be synthesised (Scheme 132).



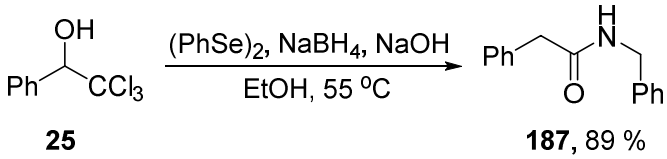
Scheme 132 Preparation of N^1-phenyl-N^1-benzylpropane-1,3-diamine **185**.

Following this the Jocic-type reaction of 1,1,1-trichloro-4-phenylbutan-2-ol **25** with **185** gave the corresponding amino-amide **186** in an 18 % yield. Subsequent removal of the benzyl groups by hydrogention using ammonium formate over palladium gave **181** in a good 60 % yield (Scheme 133). Comparison of the ^{1}H NMR spectra confirmed that we had correctly assigned the regio-chemistry of the product (*S*)-**181** from the Jocic-type reaction (Scheme 131).



Scheme 133 Independent synthesis of **181**.

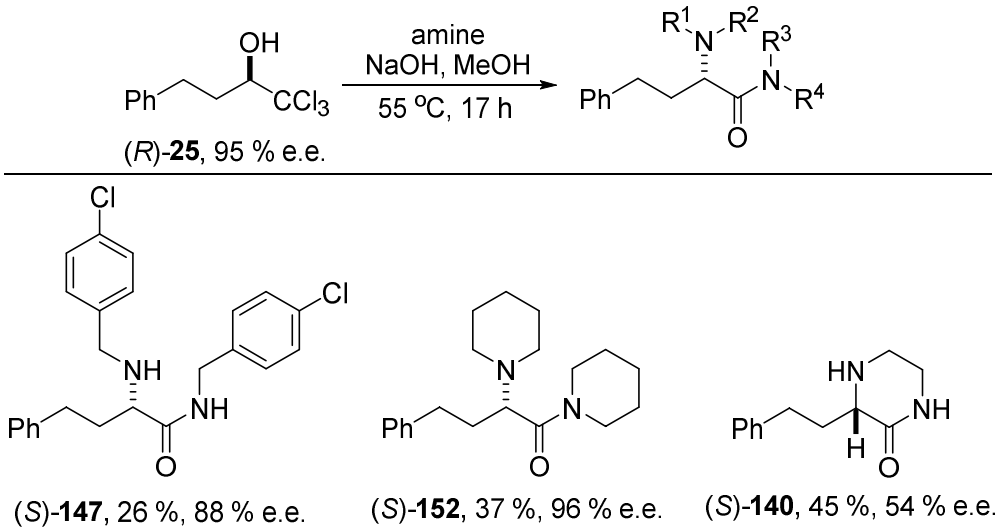
In **2.4.1** and **2.4.2** the synthesis of medicinally relevant building blocks such as various enantiomerically enriched amino-amides, piperazin-2-ones and diazepan-2-ones has been described using the biphasic conditions with phase transfer catalyst benzyltriethylammonium chloride. The products have been isolated in good yields and excellent enantiomeric excesses. With a view to remove the requirement of the phase transfer catalyst and the use of dichloromethane, an avoided solvent in scale-up in the pharmaceutical industry,[176] we wanted to explore methanol or ethanol as solvents, as Snoden *et al*. did for the synthesis of compounds such as **187** (Scheme 134).[92, 93, 95]



Scheme 134 Monophasic conditions for Jocic-type reactions with a selenium nucleophile.

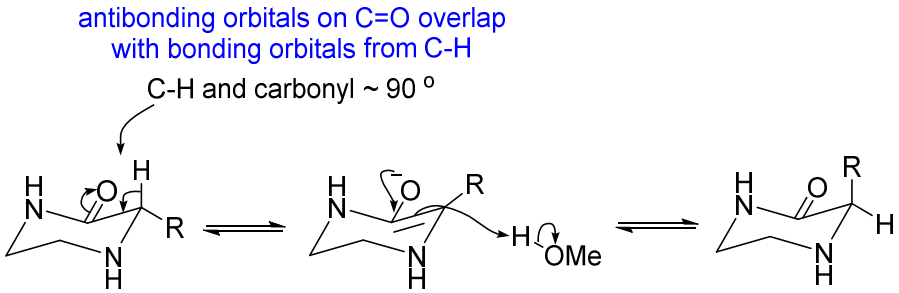
2.4.3 Jocic-type Reactions with Amines and Bis-amines in Methanol.

The reactions of enantiomerically enriched (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** with 4-chlorobenzylamine, piperidine and 1,2-ethylenediamine in methanol and sodium hydroxide at 55 °C gave the corresponding products (*S*)-**147**, (*S*)-**152** and (*S*)-**140** with strikingly different enantiomeric excesses (Scheme 135).



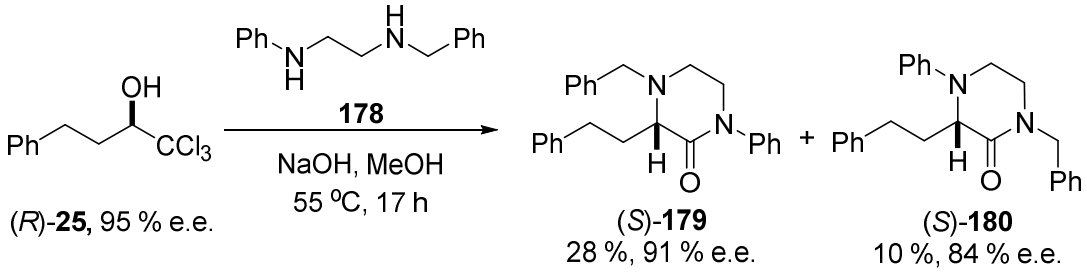
Scheme 135 Stereospecific Jocic-type reactions in methanol at 55 °C.

The reaction with 4-chlorobenzylamine gave (*S*)-**147** in poor yield and good enantiomeric excess. Similarly the reaction with piperidine gave (*S*)-**152** in poor yield and excellent enantiomeric excess. Furthermore the reaction with 1,2-ethylenediamine gave (*S*)-**140** in 45 % yield and a moderate 66 % e.e., which is a drop of 34 % e.e. compared with the biphasic PTC conditions. This significant drop in enantioselectivity could be attributed to the high reaction temperature and the mono-phasic conditions leading to an increased rate of racemisation (Scheme 136).



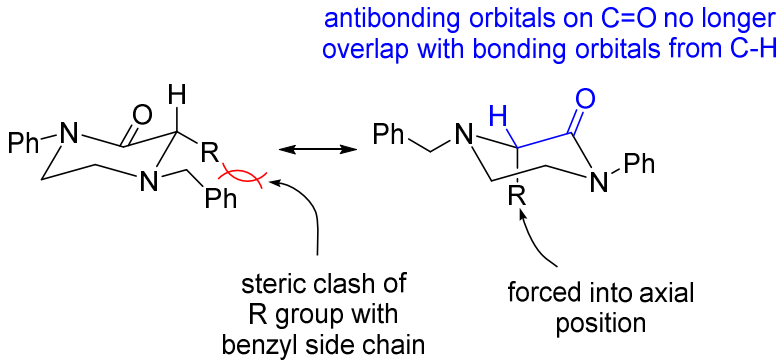
Scheme 136 Conformation of (*S*)-**140** and mechanism for racemisation.

In spite of the poor enantioselectivity here, the Jocic-type reaction with N^1-phenyl-N^2-benyzl-ethylenediamine **178** and (*R*)-1,1,1-trichloro-4-phennylbutan-2-ol (*R*)-**25** gave both regio-isomers (*S*)-**179** and (*S*)-**180** in good enantiomeric excess (Scheme 137).



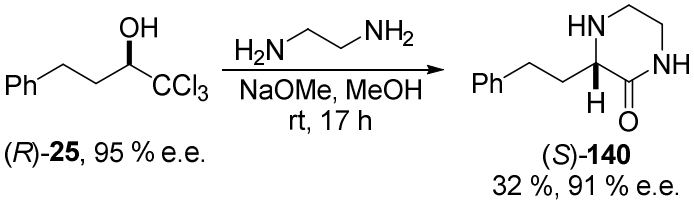
Scheme 137 Jocic-type reaction with di-substituted diamine with sodium hydroxide in methanol.

Even though there is only minimal racemisation it is significantly less than that reported for (*S*)-**140** (Scheme 135). This could be attributed to the increase in steric bulk of the substituent on the amino-nitrogen (Scheme 138).



Scheme 138 Conformations of di-substituted piperazin-2-one (*S*)-**179**.

Decreasing the reaction temperature and using sodium methoxide as the base allowed for the synthesis of (*S*)-3-phenethylpiperazin-2-one (*S*)-**140** with a much higher 91 % e.e., but only 32 % yield (Scheme 139).



Scheme 139 Synthesis of (*S*)-**140** using sodium methoxide in methanol.

In spite of decreasing the reaction temperature from 55 ºC to room temperature there was still a small amount of racemisation, which could indicate that the monophasic conditions could also be playing a role in the lower enantiomeric excesses.

2.5 CONCLUSIONS

In this Chapter the synthesis of amino-amides and related 6- or 7-membered rings *via* Jocic-type reactions has been shown in good yields and excellent enantioselectivities from enantiomerically enriched trichloromethyl alcohols (see Chaper 1). The scope of this transformation was highlighted from the reactions with unsymmetrical monosubstituted diamines and also one disubstituted diamine. Both regio-isomers from the Jocic-type reactions with unsymmetrical diamines are useful building blocks in the pharmaceutical industry. Fortunately, the minor regio-isomers can be prepared in good yields and enantiomeric excesses from the alkylation of the unsubstituted piperazin-2-one and diazepan-2-one, leading to general routes for the synthesis of both regio-isomers. Furthermore, using methanol and sodium hydroxide, or sodium methoxide, led to improved conditions for scale-up, but particularly compramised yields and enantiomeric excesses.

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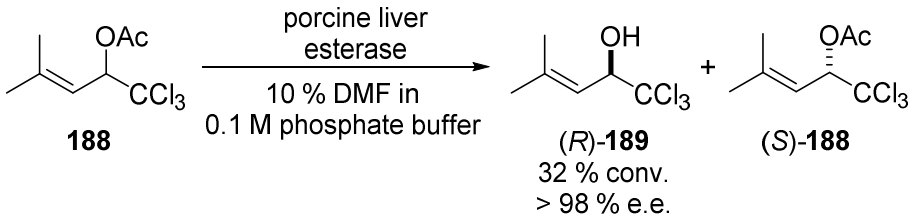
CHAPTER 3 – Enzymatic Hydrolysis of Trichloromethyl Acetates.

3.1 INTRODUCTION

Following our interest in the synthesis of enantiomerically enriched trichlorocarbinols (Chapter 1) and their subsequent use in Jocic-type reactions (Chapter 2) we hoped that the transformation reported by Fishman and coworkers could be applied to a wider range of substrates (Scheme 140).[1] The authors showed that an allylic trichlorocarbinol could be synthesised in high enantiomeric excess from the enzymatic hydrolysis of its corresponding racemic allylic acetate using porcine liver esterase (PLE).[1]



Scheme 140 Enzymatic resolution of a racemic trichloromethyl acetate to give the corresponding (*R*)-alcohol (*R*)-**189** in high enantiomeric excess.

We were particularly interested since this could provide a route for the synthesis of enantiomerically enriched allylic trichlorocarbinols, which were previously achieved in low enantiomeric excesses and as mixtures with their corresponding saturated analogues using ruthenium catalysed asymmetric transfer hydrogenation (see Chapter 1). Due to the increase in prices and concerns over the long term supply of precious metals there is a demand for alternative catalysts that are inexpensive and relatively environmentally benign.[2] Therefore we wanted to explore the scope of this enzymatic transformation by removing the unsaturation, in order to provide a general, more environmentally friendly synthesis of enantiomerically enriched trichlorocarbinols.

Since the use of enzymes in synthetic chemistry has been widely investigated there are several excellent reviews in this area and it is therefore beyond the scope of this report to discuss it further.[3-22] Section **3.1.1** will briefly discuss some of the enzymatic resolutions from the literature using PLE.

3.1.1 Enzymatic Transformations Using PLE.

PLE is a serine type of esterase that is known to catalyse the stereoselective hydrolysis of a wide variety of esters.[3] The commercially available PLE contains several isoenzymes,[23, 24] which have been shown in some cases to behave differently in terms of substrate specificity, therefore it is important to fully analyse the products of the reactions.[25] The absence of an X-ray structure of PLE means that the exact structure of the enzyme's active site is unknown. Amongst the active site models for PLE described in the literature[26, 27] the one reported by Jones and coworkers[28] is the most broadly used (Figure 45).[3]

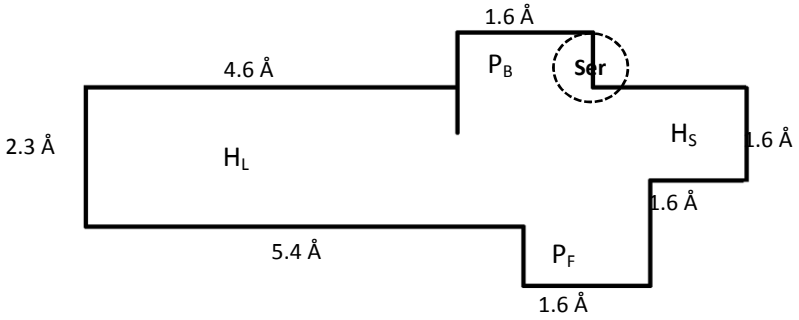
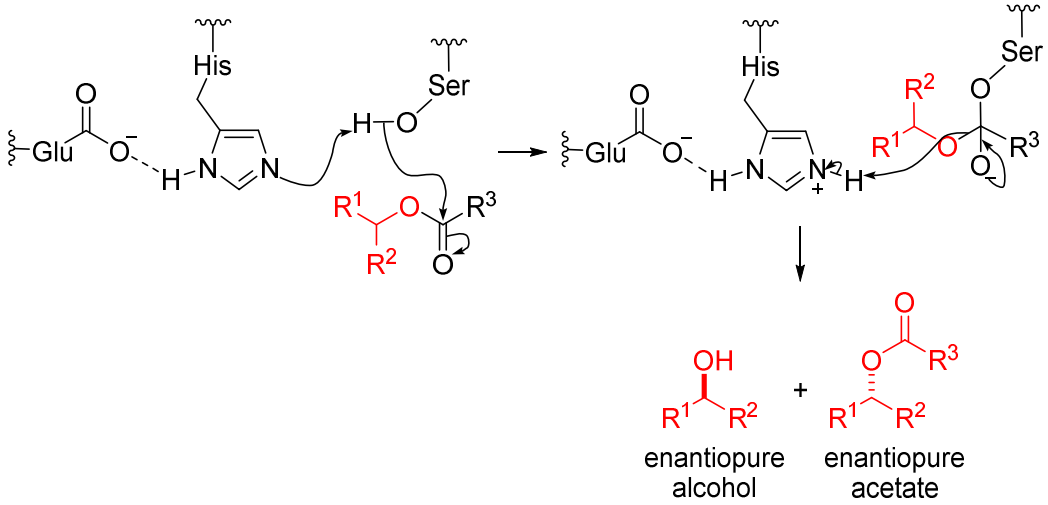


Figure 45 Jones' active-site model for PLE.

By comparison of the X-ray crystal structure data of closely related PLE analogue rabbit liver carboxyl esterase it is thought that the substrate molecules must fit into to binding pocket of the enzyme active-site so that it interacts with a catalytic triad consisting of a serine, histidine and glutamic acid.[29] The early lock – key model proposed by Emil Fischer[30] suggested that the rigid nature of an enzyme active site would allow only one of the two enantiomers to fit leading to excellent enantioselectivities. Alternatively Koshland's induced fit model[31] suggests that the reactive substrate causes a change in the three-dimensional relationship of the amino acids in the active site.[32] This may not

work as well for each enantiomer which can lead to excellent enantiofacial selectivity. The proposed mechanism of ester cleavage is shown in Scheme 141.



Scheme 141 Proposed mechanism for the enzymatic resolution of racemic acetates.

Until 1984 the use of esterases in synthetic organic chemistry was fairly limited. Since the concentration of water in the essential aqueous solutions was high and that of the ester substrate is low, often poor yields were achieved.[33] Additionally, since most of the esters required by organic chemists are poorly soluble in water, aqueous solutions could only be used at low concentrations which also lead to low yields.[33] Attempts to overcome this problem were previously unsuccessful since the addition of organic cosolvents led to the severe loss of enzymatic activity.[34] In 1984, a novel approach to the use of esterases was reported which overcame these problems and hence narrow substrate specificity.[33] Since enzymes are insoluble in water-immiscible organic solvents[35] a method using a biphasic-aqueous solution was developed.[33] This would allow the enzyme to remain dissolved in the aqueous layer and the substrate in the organic phase with the reaction taking place at the interface.[33] It was shown that this was a successful method giving enantiopure alcohols in excellent yields and enantioselectivities, which revolutionised the use of esterases in organic chemistry.[33, 36]

Since, there has been an extensive use of PLE in synthetic chemistry for the preparation of chiral building blocks. More commonly though PLE is used for the resolution of esters to give enantiopure carboxylic acids (**190**-**193**, Figure 46).[3, 26, 37-39]

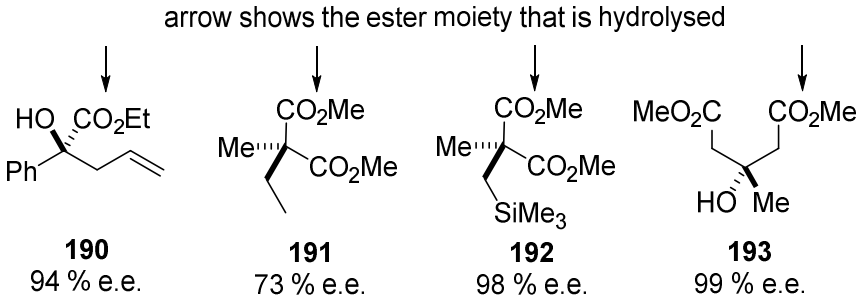


Figure 46 Synthesis of enantiomerically enriched acids from their corresponding esters using PLE.

Aside from the extensive use of PLE for the synthesis of enantiomerically enriched carboxylic acids, there are a few examples in the literature for the resolution of esters to give enantiomerically enriched alcohols (**194**-**196**, Figure 47).[37, 40, 41]

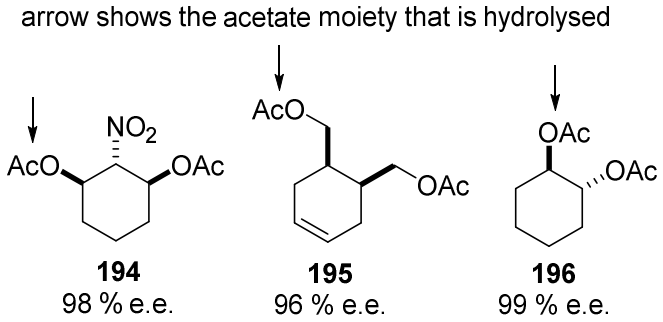
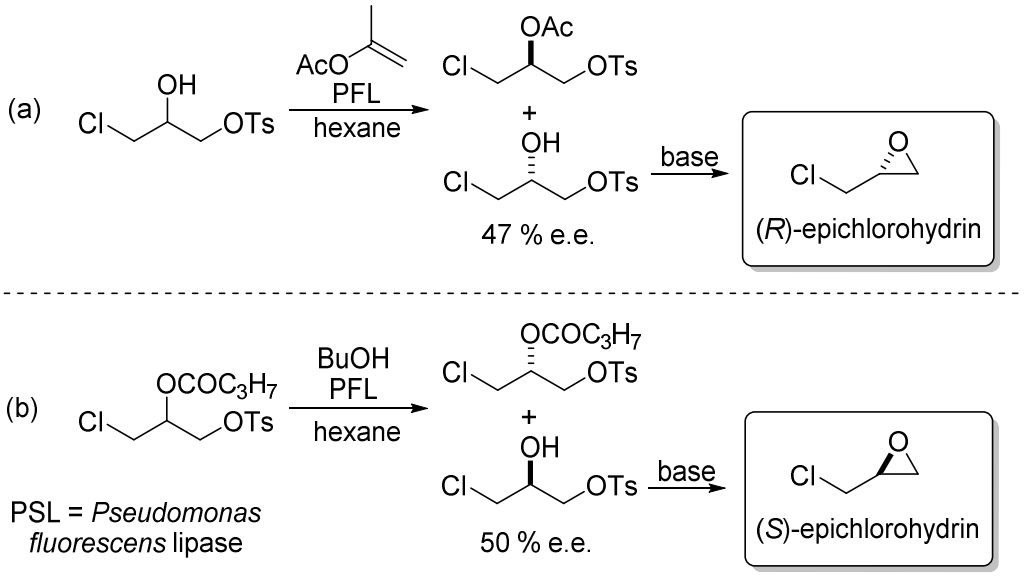


Figure 47 Synthesis of enantiomerically enriched alcohols from their corresponding acetates using PLE.

3.1.2 Enzymatic Resolutions with Enzymes Other Than PLE.

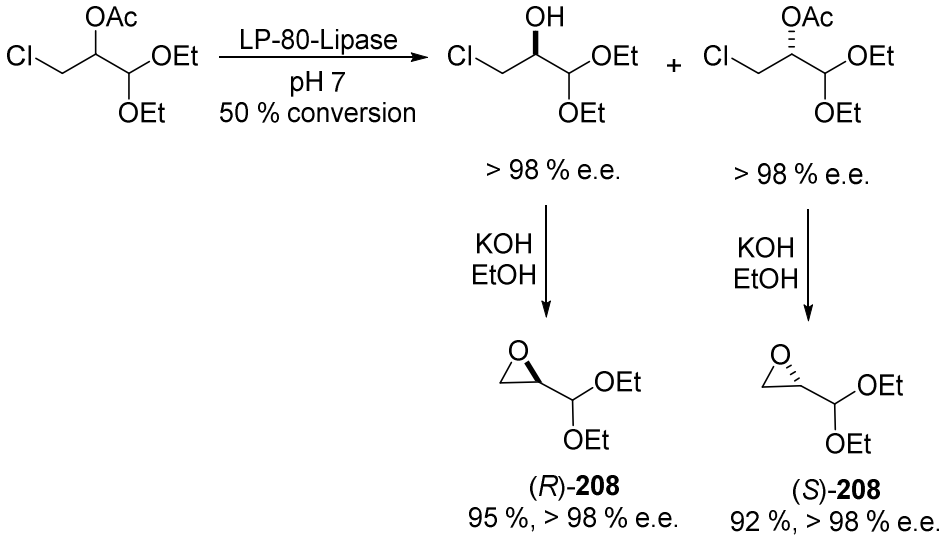
There have been several reports in the literature for the use of other lipases;[42] amongst the most common are porcine pancreatic lipase (PPL)[5, 43-48] and *Candida rugosa* lipase (CRL).[49, 50] In the literature there are a few examples of acetates bearing at least one α-halogen atom, which are somewhat related analogues to the trichloromethyl acetates we wanted to enzymatically hydrolyse.[3]

In 1989 Chen and coworkers used a lipase-mediated formation for the synthesis of a precursor to (*R*)-epichlorohydrin (a, Scheme 142), a highly reactive precursor in synthesis.[51] Furthermore, the authors reported the synthesis of the (*S*)-enantiomer of epichlorohydrin by enzyme catalysed ester hydrolysis (b, Scheme 142).[51]



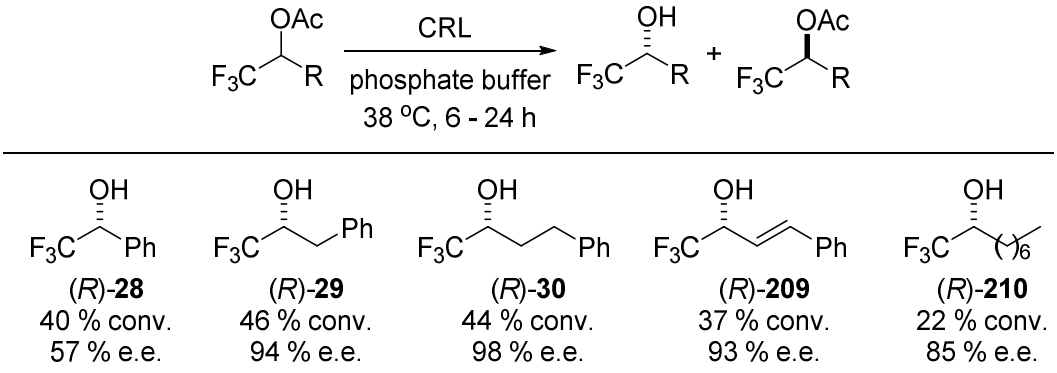
Scheme 142 Synthesis of (a) (*R*)-epichlorohydrin by an enzymatic hydrolysis and (b) (*S*)-epichlorohydrin by an enzyme catalysed ester formation.

Shortly after, Wong and coworkers noticed that α-fluoro and chloro acetates could be enzymatically resolved to give both the hydrolysed alcohol product and remaining acetate in greater than 98 % e.e at 50 % conversion.[52] The α-chloro products were of great use since they could be converted into 1,2-epoxides (*R*) and (*S*)-**208** (Scheme 143), which are useful building blocks in organic synthesis.[53]



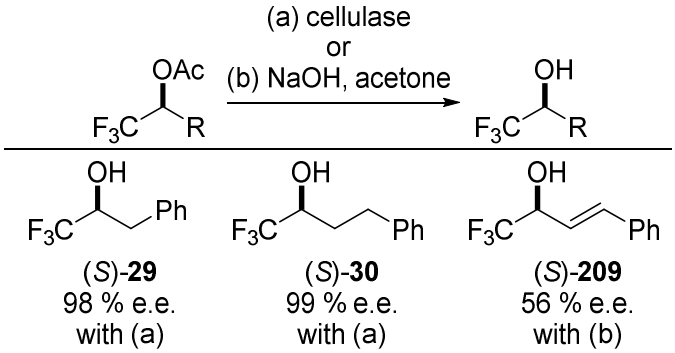
Scheme 143 Synthesis of enantiopure 1,2-epoxides from enzymatic ester hydrolysis of α-chloroacetates.

Lin and coworkers reported the preparation of enantiopure trifluorocarbinols using CRL, which are close analogues to trichlorocarbinols.[54] Scheme 144 shows the formation of a range of (*R*)-trifluorocarbinols ((*R*)-**28**-**30**, **209** and **210**) in excellent conversions and enantiomeric excesses.



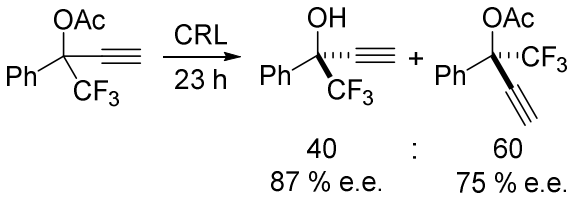
Scheme 144 CRL catalysed ester hydrolysis of trifluoromethyl acetates.

More importantly, the corresponding (*S*)-trifluorocarbinols ((*S*)-**29**, **30** and **209**) are also isolatable in excellent enantiomeric excesses by hydrolysing the isolated (*S*)-trifluoromethyl acetates (Scheme 145).[54]



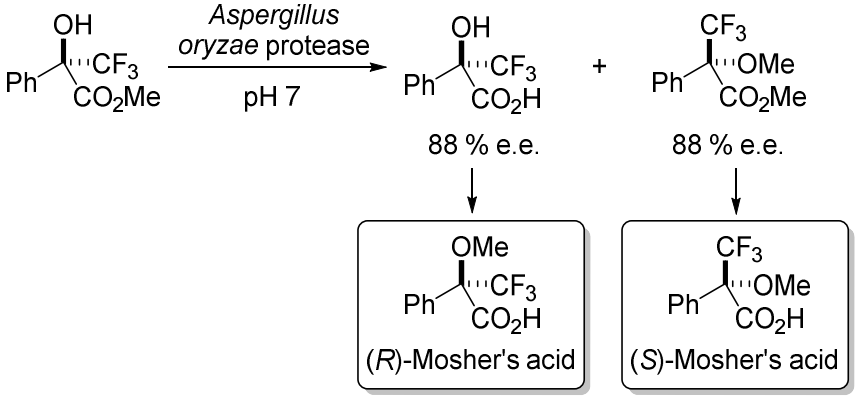
Scheme 145 Ester hydrolysis to form the corresponding (*S*)-trifluorocarbinol.

Following this, O'Hagan and coworkers showed that tertiary trifluoromethyl acetates could be resolved using CCL as shown in Scheme 146.[55]



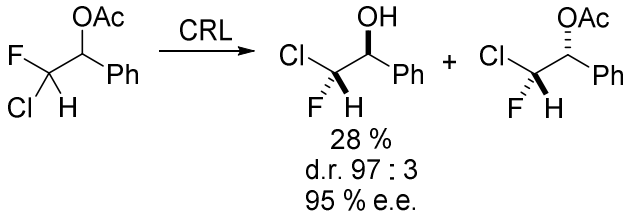
Scheme 146 Enzymatic ester hydrolysis of tertiary trifluoromethyl acetates.

Other monofluoro- and trifluoromethyl-containing acetates have been resolved enzymatically in the literature.[56] For example, the synthesis of both enantiomers of the commonly used ^{1}H NMR chiral derivatising agent Mosher's acid[57, 58] is possible using *Aspergillus oryzae* protease (Scheme 147).[59]



Scheme 147 Enzymatic ester hydrolysis of tertiary trifluoromethyl acetate for the synthesis of both enantiomers of Mosher's acid.

Other halogen-containing acetates have been shown to be enzymatically hydrolysed using CRL.[60] For example, the synthesis of chlorofluoromethyl alcohols are possible in excellent diastereomeric ratios (**Scheme 148**).[60]



Scheme 148 Synthesis of chlorofluoromethyl alcohols in excellent d.e.

With this in mind, we wanted to investigate the lipase-catalysed hydrolysis of a variety of trichloromethyl acetates, which are discussed in section **3.2**.[1]

3.2 RESULTS AND DISCUSSION

3.2.1 Selection of the Enzymes and Substrates.

Since we wanted to investigate the scope of this reaction we chose to synthesise a wide variety of trichlorocarbinols. There were a few obvious modifications that could be made to the original unsaturated acetate **189**, i.e. the addition of any further groups (Figure 48, in blue) or the reactions with non-allylic trichloromethyl acetates.

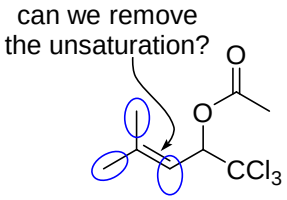
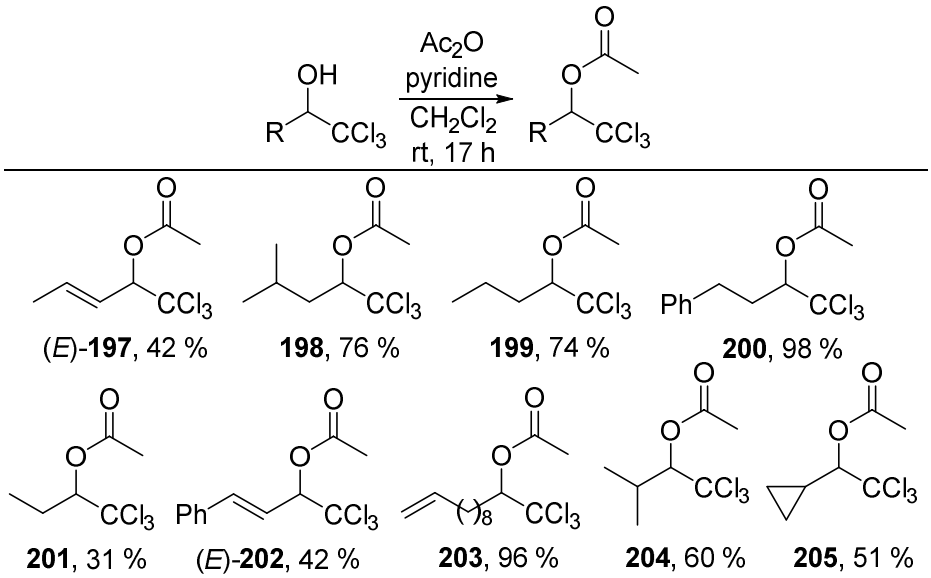


Figure 48 Proposed modifications of the unsaturated substrate **188**.

Therefore, the chosen racemic trichloromethyl acetates were prepared from their corresponding trichlorocarbinols (Scheme 149). Upon screening a variety of other enzymes such as Lipase M,[61] Lipase AKG[62] and porcine pancreatic lipase (PPL) only PLE showed activity for the ester hydrolysis of **188**. Also, polymer supported enzymes such as Novozym 435[63] and Lipozym IM[64] showed no activity as did lipases from the microorganisms *Rhizopus arrhizus*, *Mucor miehei* and *Candida lipolytica*. Hence, at this point reactions using PLE were investigated.



Scheme 149 Synthesis of racemic trichloromethyl acetates from their relevant alcohols.

3.2.2 Enantioselectivity of Enzyme Catalysed Reactions.

In an enzyme catalysed kinetic resolution the enantioselectivity is normally expressed as the E value, which corresponds to the ratio of specificity constants.[3, 13, 65, 66] The E value for irreversible enzymatic transformations are generally calucated using Equations 1 and 2.[3, 13, 65, 66]

Where the conversion is lower than 50 %:

$$\mathrm{E} = \frac{\ln[1 - \mathrm{c}(1 + \mathrm{e.e.(p)})}{\ln[1 - \mathrm{c}(1 - \mathrm{e.e.(p)})} \qquad \textbf{Equation 1}$$

Where the conversion is greater than 50 %:

$$\mathrm{E} = \frac{\ln[1 - \mathrm{c})(1 - \mathrm{e.e.(s)})}{\ln[1 - \mathrm{c})(1 + \mathrm{e.e.(s)})} \qquad \textbf{Equation 2}$$

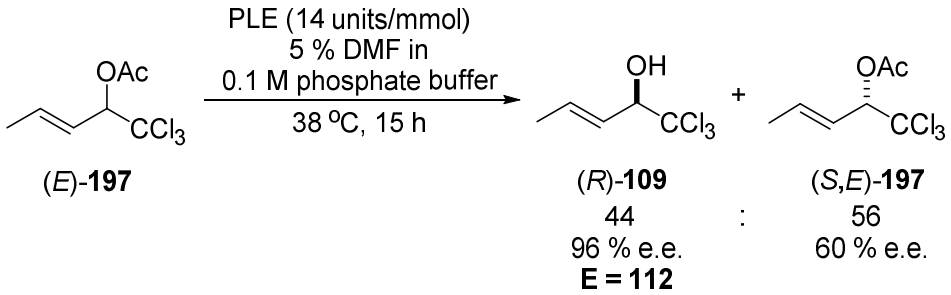
Where, c = conversion (%)/100, e.e.(p) = e.e. of product/100 and e.e.(s) = e.e. of remaining starting material/100.

Reaction conversions in the next section were calculated from the crude ^{1}H NMR of the extracted organics which were concentrated *in vacuo*. Due to the volatility of the trichloromethyl acetates synthesised the conversions should only be treated as estimates.

Due to the sensitivity of E values to conversion, calculations using the equations above were shown to be inconsistent.

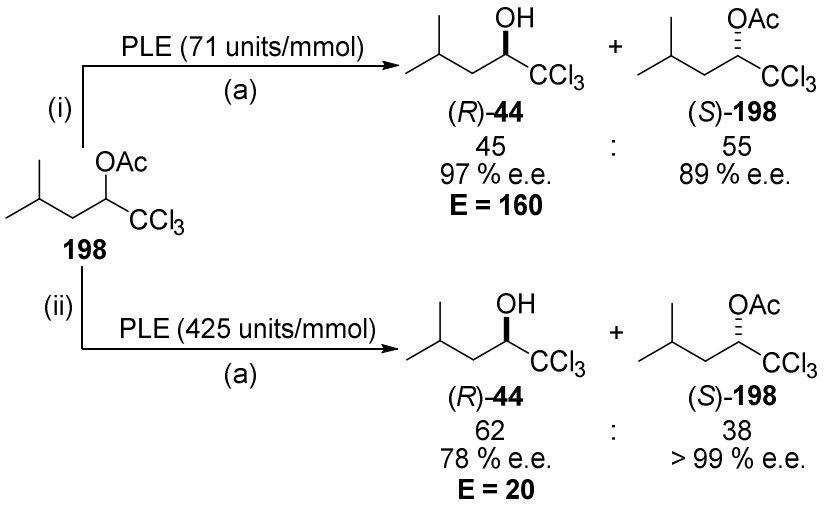
3.2.3 Enzymatic Resolutions with PLE and DMF as the Cosolvent.

Removal of one of the methyl groups from the original substrate (Figure 48) to give (*E*)-**197** and the subsequent resolution with PLE gave the desired trichlorocarbinol in good conversion (44 %) and an excellent 96 % e.e. (Scheme 150).



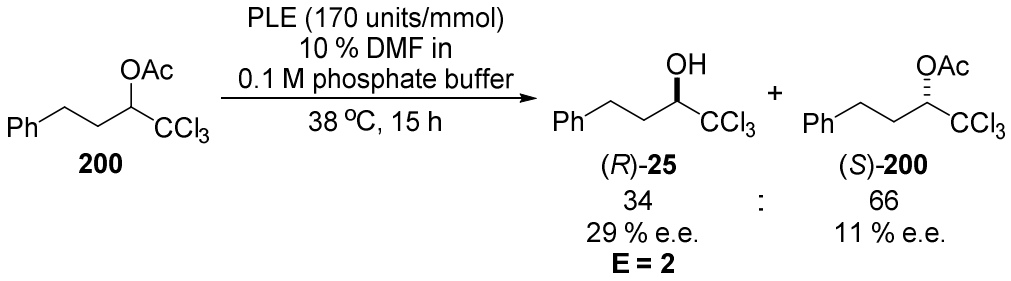
Scheme 150 PLE catalysed ester hydrolysis of racemic (*E*)-**197** with DMF.

We then wanted to investigate the importance of the substrate being an allylic acetate. Reaction of the saturated version (*E*)-**189** gave the corresponding enantiomerically enriched (*R*)-alcohol (*R*)-**44** in 45 % conversion and excellent 97 % e.e. (Scheme 151, (i)). The (S)-acetate (*S*)-**198** being left in 89 % e.e. indicated that it may be possible to isolate both enantiomeric series, the (*R*)-alcohol and (*S*)-acetate, from controlling the conversion of the reaction. In fact, we showed this to be true by pushing the reaction to 62 % conversion (Scheme 151, (ii)).



Scheme 151 Synthesis of (i) (*R*)-**206** and (ii) (*S*)-**198** in excellent enantiomeric excesses using PLE and DMF as a cosolvent.

We also wanted to analyse the reactions of larger substrates, beginning with **200**. Despite the fairly decent conversion the enantiomeric excess of both (*R*)-**25** and (*S*)-**200** were poor (Scheme 152), indicating that enzyme's active site poorly discriminates between the enantiomers of **200**.

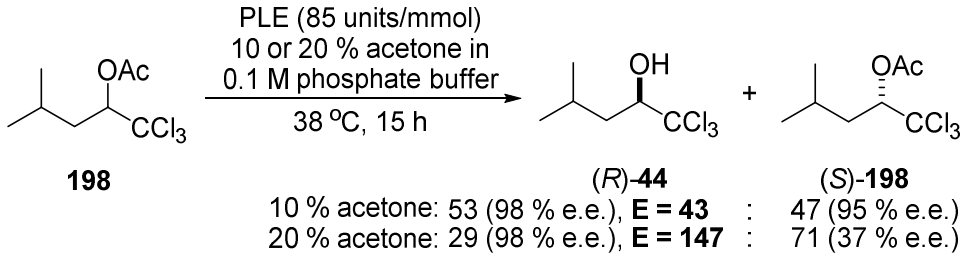


Scheme 152 PLE catalysed ester hydrolysis of **200** with DMF.

Due to the increasing effort to move towards using more environmentally friendly, less toxic and easier to remove solvents[67-69] we wanted to replace DMF in these enzymatic transformations. Also, it has been reported that different solvent systems can have an enormous effect on the conversion and stereocontrol of the reaction.[1] Acetone is a preferred alternative due to its ease of removal and disposal as well as the decreased health risk compared with DMF.[67] With this in mind we investigated a series of PLE catalysed ester hydrolysis reactions with different racemic trichloromethyl acetates using acetone as the cosolvent in 0.1 M phosphate buffer.

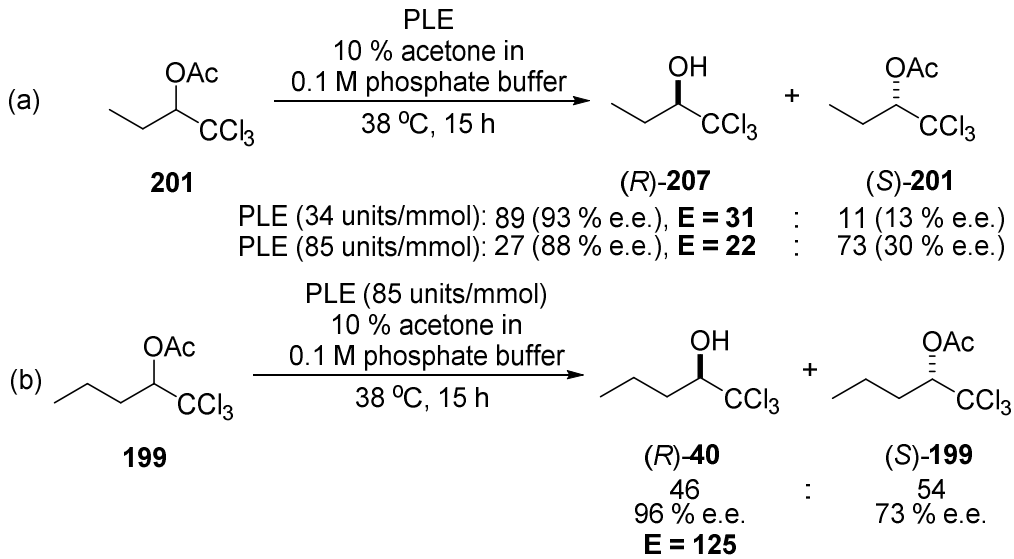
3.2.4 Enzymatic Resolutions with PLE and Acetone as the Cosolvent.

The resolution of saturated **198** gave both the corresponding (*R*)-**206** and (S)-**198** in excellent enantiomeric excess with a conversion of 53 % (Scheme 153). Increasing the amount of acetone in the reaction from 10 to 20 % led to a decreased rate of acetate hydrolysis, whilst maintaining the high enantiomeric excess of (*R*)-**206** (Scheme 153).



Scheme 153 Enzymatic resolution of racemic **198** with acetone and PLE.

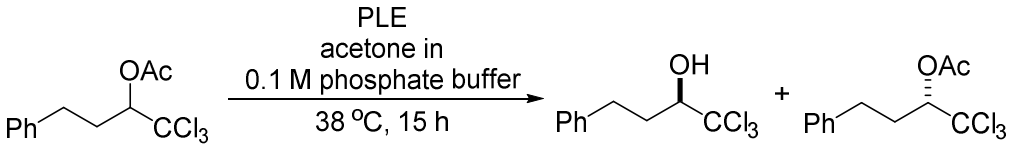
When decreasing the size of the R-group the corresponding (*R*)-alcohols could still be formed in high enantiomeric excess as shown with the resolution of **201** and **199** (Scheme 154).



Scheme 154 Enzymatic resolution of racemic (a) **201** and (b) **199** with acetone and PLE.

The stereocontrol of the hydrolysis of **200** was much improved using acetone (Scheme 155) as the cosolvent compared with that of DMF (Scheme 152). The best conditions for the formation of (*R*)-**25** were with 42.5 units of PLE and 10 % acetone in 0.1 M

phosphate buffer, which gave the desired product in 40 % conversion and 77 % e.e. (Scheme 155).

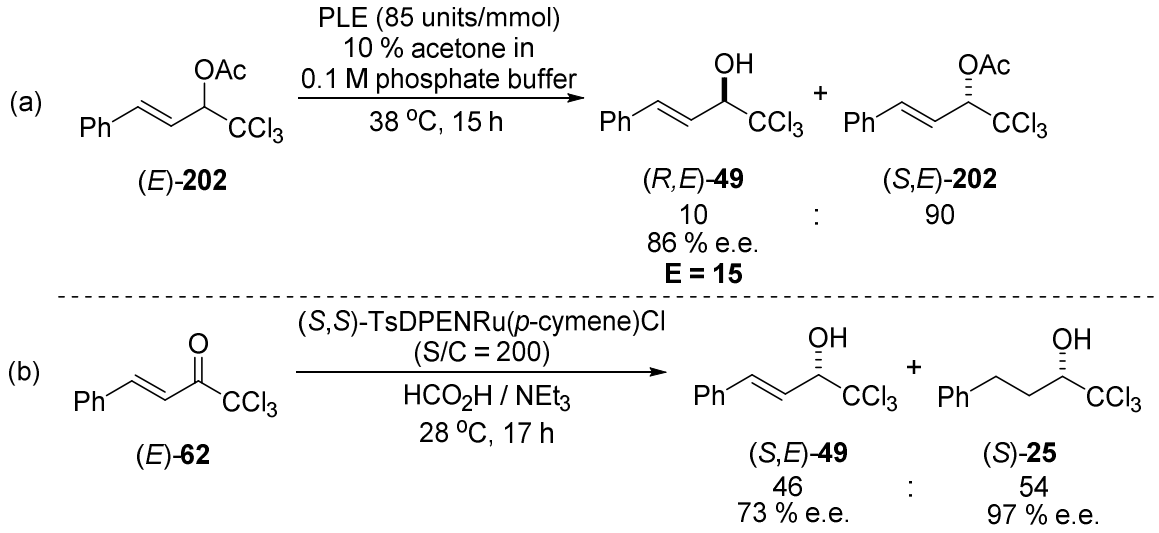


200 (*R*)-**25** (*S*)-**200**

PLE (34 units/mmol), 10 % acetone:	34 (71 % e.e.), **E = 8**	:	66 (39 % e.e.)
PLE (85 units/mmol), 20 % acetone:	40 (77 % e.e.), **E = 13**	:	60 (41 % e.e.)
PLE (85 units/mmol), 5 % acetone:	63 (72 % e.e.), **E = 2**	:	37 (36 % e.e.)
PLE (340 units/mmol), 10 % acetone:	56 (53 % e.e.), **E = 9**	:	44 (76 % e.e.)
PLE (340 units/mmol), 20 % acetone:	63 (69 % e.e.), **E = 2**	:	37 (82 % e.e.)

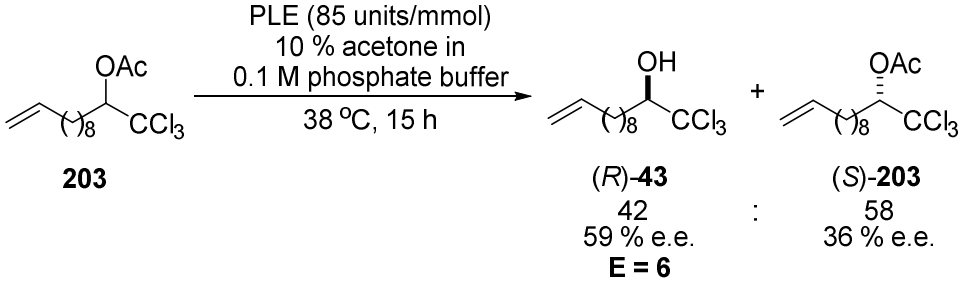
Scheme 155 Enzymatic resolution of racemic **200** with acetone and PLE.

Despite this improvement the enantiomeric excess of (*R*)-**25** is still not as high as that from the ruthenium catalysed asymmetric transfer hydrogenation of the corresponding ketone, which gave (*R*)-**25** in 95 % e.e. (Chapter 1). Since reactions with the saturated alcohol **200** gave poor results the enzymatic hydrolysis of the unsaturated (*E*)-**202** was attempted (Scheme 156). Despite the low conversion, (*R*,*E*)-**49** was formed in a good 86 % e.e. (a, Scheme 156), which is higher than that of the saturated analogue (*R*)-**25** (77 % e.e., Scheme 155). In this particular case the enantiomeric excess of (*R*,*E*)-**49** is far better with the enzymatic resolution using PLE compared with the ruthenium catalysed asymmetric transfer hydrogenation (Scheme 156).



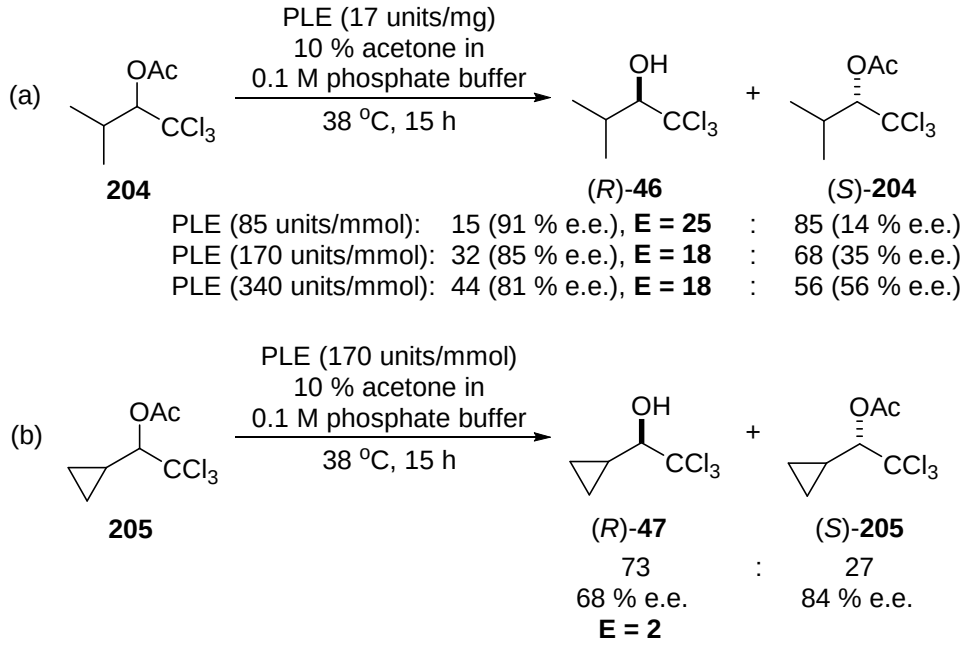
Scheme 156 (a) Enzymatic resolution of unsaturated (*E*)-**202** compared with (b) the asymmetric transfer hydrogenation of (*E*)-**62.**

The resolution of **203** with PLE gave (*R*)-**43** in good conversion however in a poor 58 % e.e. (Scheme 157), which is nowhere near as high as the 97 % e.e. produced from the ruthenium catalysed asymmetric transfer hydrogenation (see Chapter 1).



Scheme 157 Enzymatic resolution of **203** with acetone and PLE.

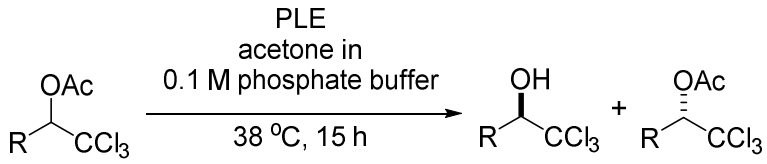
We then wanted to explore substrates with substitution at the α-position, such as 1,1,1-trichloro-3-methylbutan-2-yl acetate **204** and 2,2,2-trichloro-1-cyclopropylethyl acetate **205** (Scheme 158).



Scheme 158 Enzymatic resolution of branched (a) **204** and (b) **205** with PLE and acetone.

The resolution of the **204** gave (*R*)-**46** in good enantiomeric excess (81 – 91 % e.e.), however we found that more PLE was required compared with the previous reactions. Also, we showed that at just 15 % conversion (*R*)-**46** could be formed in much higher enantiomeric excess (91 % e.e.) compared with that at 44 % conversion (81 % e.e.). This suggests that as the (*R*)-acetate (*R*)-**204** is consumed the enantiocontrol of the hydrolysis decreases.

Since the best ruthenium catalysed asymmetric transfer hydrogenation of 2,2,2-trichloro-1-cyclopropylethan-1-one **59** gave the corresponding alcohol (*R*)-**47** in a poor 51 % e.e. (see Chapter 1) we were particularly interested in investigating the enzymatic hydrolysis of the corresponding acetate **205**. Using the PLE and acetone conditions the desired (*R*)-**47** was given in a moderate 68 % e.e. (Scheme 158). Despite the enantiomeric excess being much higher from using PLE it was still nowhere near as high as desired. The results of the enzymatic resolutions using PLE and acetone conditions described in this section are summarised in Table 10.



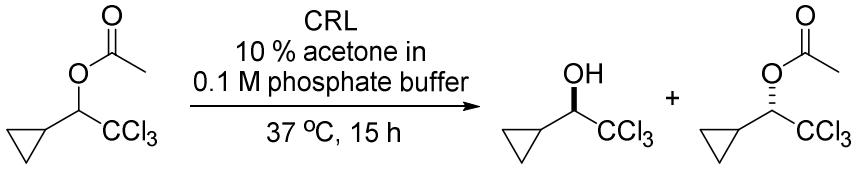
Entry	R	PLE[a,b]	Acetone %	Cpd No.	(*R*)-OH conv.[c]	(*R*)-OH e.e.[d]	Cpd No.	(*S*)-OAc conv.[c]	(*S*)-OAc e.e.[d]
1	$CH_2CH(CH_3)_2$	85	10	**44**	53	98	**199**	47	95
2	$CH_2CH(CH_3)_2$	85	20	**44**	29	98	**199**	71	37
3	CH_2CH_3	34	10	**207**	11	93	**201**	89	13
4	CH_2CH_3	85	10	**207**	27	88	**201**	73	30
5	$(CH_2)_2CH_3$	85	10	**40**	46	96	**199**	54	73
6	$(CH_2)_2Ph$	34	10	**25**	34	71[e]	**200**	66	39[e]
7	$(CH_2)_2Ph$	85	10	**25**	40	77[e]	**200**	60	41[e]
8	$(CH_2)_2Ph$	85	5	**25**	37	72[e]	**200**	63	36[e]
9	$(CH_2)_2Ph$	340	10	**25**	56	53[e]	**200**	44	76[e]
10	$(CH_2)_2Ph$	340	20	**25**	63	69[e]	**200**	37	82[e]
11	(*E*)-CH=CHPh	85	10	**49**	10	86[e]	**202**	90	-[f]
12	$(CH_2)_8CH=CH_3$	85	10	**43**	42	59	**203**	58	36
13	$CH(CH_3)_2$	85	10	**46**	15	91	**204**	85	14
14	$CH(CH_3)_2$	170	10	**46**	32	85	**204**	68	35
15	$CH(CH_3)_2$	340	10	**46**	44	81	**204**	56	56
16	cyclopropyl	170	10	**47**	73	68[e]	**205**	27	84

[a] in units/mmol. [b] 1 unit hydrolyses 1 µmol of ethyl butyrate per min. at pH 8 and 25 °C. [c] by 1H NMR of crude reaction mixture. [d] by chiral GC analysis. [e] by chiral HPLC analysis. [f] enantiomers not resolvable by chiral HPLC.

Table 10 Summary of results for the PLE catalysed hydrolysis of acetates with acetone as the cosolvent.

Efforts to improve the enantiomeric excess of (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** began with investigating alternative enzymes for the resolution of 2,2,2-trichloro-1-cyclopropylethyl acetate **205**.

Following the several reports of closely related halogen-containing acetates in the literature the use of CRL[49, 50] was explored for the enzymatic hydrolysis of 2,2,2-trichloro-1-cyclopropylethyl acetate **205**. We attempted the resolution of **205** with CRL from different suppliers (Table 11), since it has previously been shown that the activity of the same enzyme can change depending on the supplier.[1, 25]



205 (*R*)-**47** (*S*)-**205**

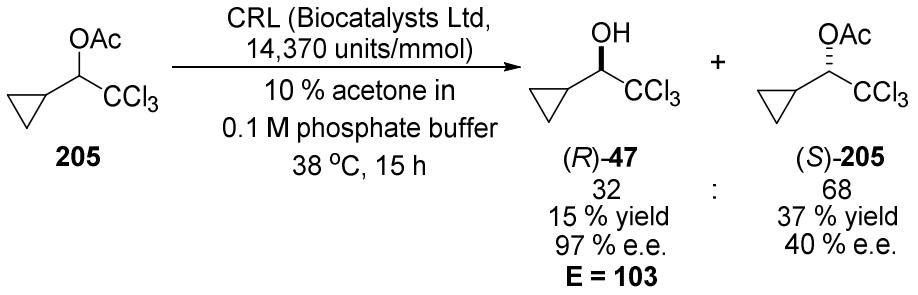
Entry	Supplier	CRL[a] units/mmol	(*R*)-OH conv.[e]	(*R*)-OH e.e.[f]	(*R*)-OAc conv.[e]	(*R*)-OAc e.e.[g]
1	Sigma Aldrich[a]	47,150	15	94	85	17
2	Sigma Aldrich[a]	94,300	27	96	73	37
3	Sigma Aldrich[a]	150,880	37	94	63	24
4	Fluka[b]	330	20	97	80	23
5	Fluka (Sol-Gel)[b,c]	1300	0	-	100	-
6	Biocatalysts Ltd[d]	14,370	32	97	68	31

[a] 1 unit liberates 1 µmol of fatty acid from olive oil at pH 7.2 and 37 °C. [b] 1 unit hydrolyses 1 µmol of oleic acid per min. at pH 8.0 at 40 °C. [c] polymer supported CRL. [d] 1 unit liberates 1 µmol of fatty acid from olive oil at pH 7.0 and 37 °C. [e] by 1H NMR of crude reaction mixture. [f] by chiral GC analysis of *n*-butyl ester. [g] by chiral GC analysis.

Table 11 Ester hydrolysis of racemic cyclopropyl trichloromethyl acetates by CRL.

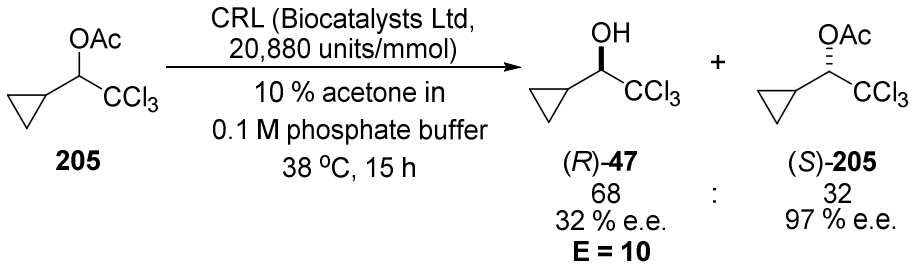
Resolution of **205** with 47,150 units/mmol of the CRL from Sigma Aldrich (entry 1) gave a low conversion of the desired (*R*)-**47** however in an excellent 94 % e.e. which is the highest enantiomeric excess achieved for this compound. Entries 2 and 3 show that

increasing the amount of CRL from Sigma Aldrich led to increased conversions and the enantiomeric excesses for (*R*)-**47** were excellent at 96 % and 97 % e.e. respectively. The CRL from Fluka showed good activity with the formation of (*R*)-**47** in 97 % e.e. (entry 4). The polymer-bound CRL from Fluka showed no apparent activity, most likely due to solubility issues (entry 5). Using the CRL from Biocatalysts Ltd (entry 6) gave (*R*)-**47** in an excellent 97 % e.e. and fairly decent conversion (32 %). Also, the remaining (*S*)-**205** was left in a good 84 % e.e., which indicated that from controlling the conversion we could isolate both enantiomeric series in excellent enantiomeric excesses. Keeping the enzymatic resolution of 2,2,2-trichloro-1-cyclopropylethyl acetate **205** under 50 % allowed (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** to be formed in high enantiomeric excess (Scheme 159).



Scheme 159 Enzyme catalysed hydrolysis of racemic **205** with CRL and acetone for the synthesis of (*R*)-**47** in high enantiomeric excess; 1 unit liberates 1 µmol of fatty acid from olive oil at pH 7.0 and 37 ºC.

Due to the chemical differences between (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** they were easily separated by silica column chromatography, which led gave (*R*)-**47** in 15 % yield and 97 % e.e. (Scheme 159).



Scheme 160 Enzyme catalysed hydrolysis of racemic **205** with CRL and acetone for the preparation of (*S*)-**205**; 1 unit liberates 1 µmol of fatty acid from olive oil at pH 7.0 and 37 ºC.

Using more CRL and hence pushing the enzymatic resolution to greater than 50 % conversion left (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in an excellent 97 % e.e. (Scheme 160). Since it was previously shown that (*R*)-**47** and (*S*)-**205** could be easily separated (Scheme 159), this gives a generic method for the efficient synthesis of (*S*)-2,2,2-trichloro-1-cyclopropylethyl (*S*)-**205** in excellent enantiomeric excess.

3.3 CONCLUSIONS

In this Chapter we have shown that biocatalysis can be used for the synthesis of enantiomerically enriched (*R*)-trichlorocarbinols and sometimes their corresponding (*S*)-acetate analogues. Due to the relatively low environmental implications associated with enzymatic catalysis such as their low toxicity, the requirement of generally mild reaction conidions and their renewable nature,[70] the methods described in this Chapter are ideal for scale-up.

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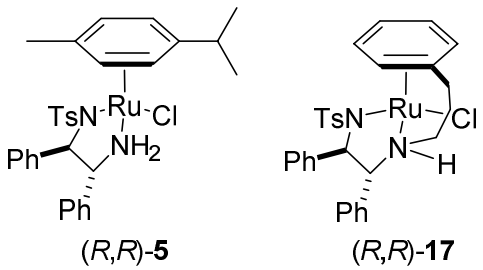
CHAPTER 4

4.1 CONCLUSIONS

The discovery of a novel directing group for asymmetric transfer hydrogenation is shown in Chapter 1 with the reduction of a variety of alkyl/trichloromethyl ketones. These asymmetric reductions gave the corresponding trichlorocarbinols in good yields and generally excellent enantiomeric excesses. The best results were achieved with reduction catalysts (*R*,*R*)-**5** and (*R*,*R*)-**17** (Figure 49). Typically the enantioselectivities were comparable with both catalysts, however for the more hindered *iso*-propyl and cyclopropyl-bearing trichloromethyl ketones the enantiomeric excesses were much higher with the 'reverse-tethered' (*R*,*R*)-**17**.

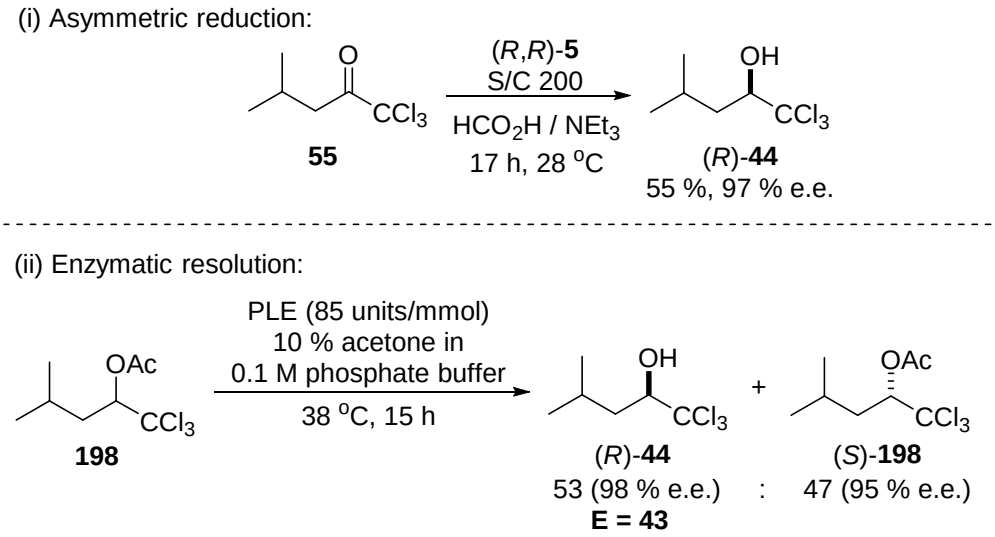


(*R*,*R*)-**5** (*R*,*R*)-**17**

Figure 49 Asymmetric transfer hydrogenation catalysts (*R*,*R*)-**5** and (*R*,*R*)-**17**.

An alternative method for the preparation of some enantiomerically enriched trichlorocarbinols was demonstrated in Chapter 3 with the enzymatic resolutions of some racemic trichloromethyl acetates. These resolutions showed that enantioselectivities as high as those in Chapter 1 could be achieved but the substrate scope was not as broad. Therefore, depending on the nature of the desired enantiomerically enriched trichlorocarbinol, the correct method should be selected. In one particular case an enzymatic resolution using CRL gave (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** in 97 % e.e., which is far superior than that from the asymmetric transfer hydrogenation of the corresponding ketone (51 % e.e). Also, in cases where the enantiomeric excesses of the trichlorocarbinols were comparable with

both methods, such as the example in Scheme 161, the enzymatic resolution route could offer an advantage by potentially delivering the (*S*)-trichloromethyl acetate and (*R*)-trichlorocarbinol in high e.e. from the same reaction, both of which are reactive intermediates in Jocic-type reactions.



Scheme 161 Comparison of the synthesis of (*R*)-**44** *via* (i) asymmetric transfer hydrogenation or (ii) enzymatic resolution.

Furthermore, using enzymes such as PLE and CRL offers a cheaper alternative than using the ruthenium catalysts.

Some of the enantiomerically enriched trichlorocarbinols were used to synthesise a variety of amino-amides, such as piperazin-2-one, diazepan-2-one and 3,4-dihydroquinoxalin-2-one-derived compounds, which are useful pharmaceutical building blocks (Chapter 2, Figure 50).

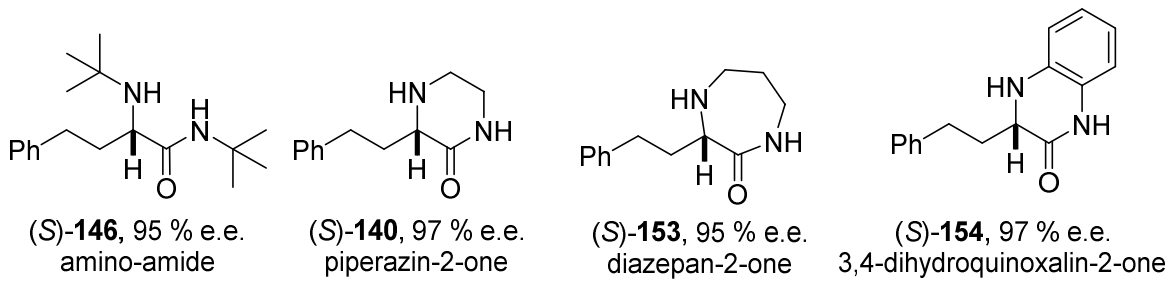
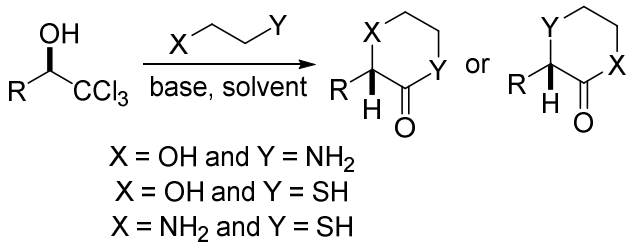


Figure 50 Useful pharmaceutical building blocks; amino-amides, piperazin-2-ones, diazepan-2-ones and 3,4-dihydroquinoxalin-2-ones.

The good yields, excellent enantioselectivities and mild reaction conditions make this route ideal for the preparation of a wide variety of derivatives.

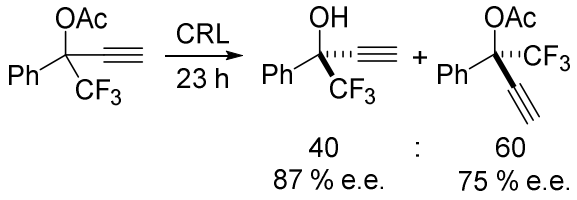
4.2 FUTURE WORK

In order to widen the scope of asymmetric Jocic reactions other nucleophiles described in Chapter 2 must be explored. Also, competition experiments between bis-nucleophiles such as those shown in Scheme 162 should be investigated.



Scheme 162 Other bis-nucleophiles to be investigated in asymmetric Jocic-type reactions.

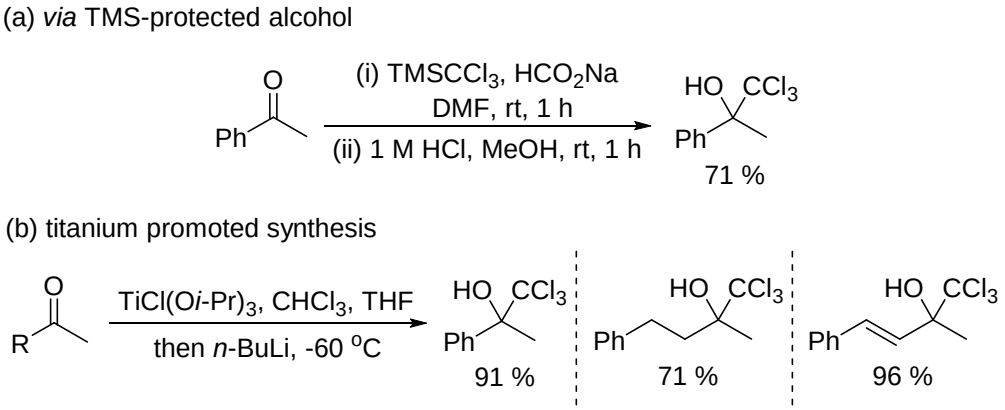
As discussed in Chapter 3, the kinetic resolution of racemic esters with hydrolytic enzymes is a well-established procedure for the synthesis of enantiomerically enriched secondary alcohols. Despite the preparation of tertiary alcohols in high e.e. being rare there are a few examples in the literature,[1, 2] one of which contains the trifluoromethyl group (Scheme 163).



Scheme 163 Enzymatic resolution of trifluoromethyl-bearing tertiary acetate.

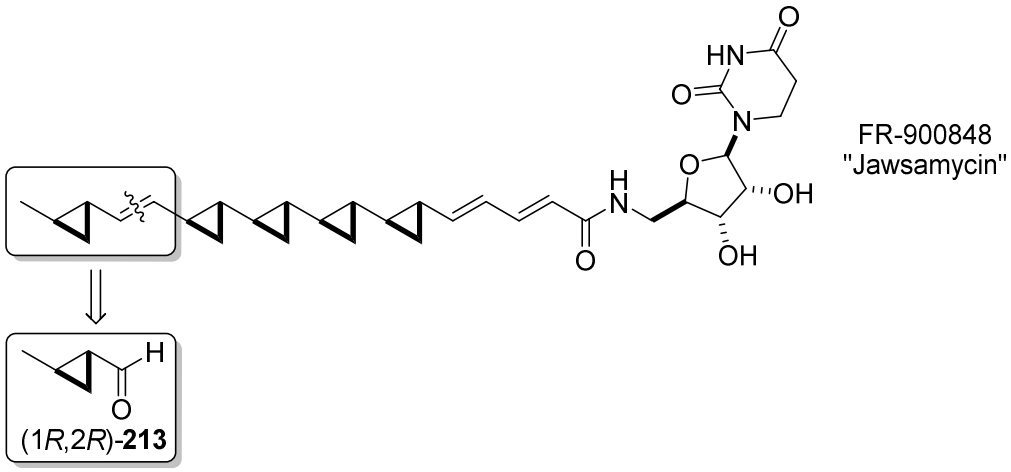
With this in mind the preparation of enantiomerically enriched tertiary trichlorocarbinols could be explored using this route. The method used in Chapter 1 for the synthesis of trichlorocarbinols is limited to reactions with aldehyde substrates.[3] Furthermore, the base promoted addition of chloroform to carbonyl compounds is

generally applied to only non-enolisable substrates.[4-9] Tertiary trichlorocarbinols can however be synthesised *via* the deprotection of the corresponding TMS-protected alcohols and the more recent titanium promoted synthesis reported by Li and coworkers (Scheme 164).[9, 10]



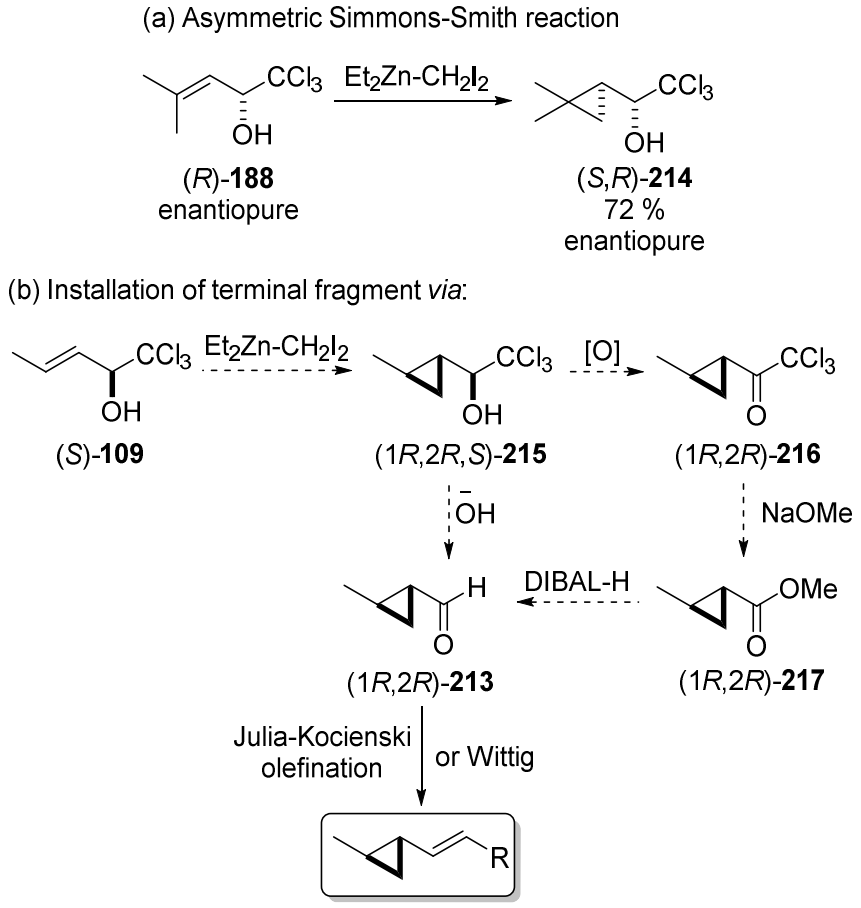
Scheme 164 Methods for the synthesis of racemic tertiary trichlorocarbinols.

Additionally, since allylic alcohols and acetates can be synthesised in high e.e. from the enzymatic resolution of their corresponding racemic acetates using PLE, further reactions of these substrates could also be explored. Within the Fox group a suitable synthesis of the terminal fragment (*R*,*R*)-**213** is required for the synthesis of natural product FR-900848 “Jawsamycin” (Scheme 165).



Scheme 165 Disconnection of Jawsamycin to give (1*R*,2*R*)-**213**.

Using the previously reported asymmetric Simmons-Smith reaction (a, Scheme 166) we want to synthesise (*R*)-**213** and subsequently react it with another fragment from the Jawsamycin framework (b, Scheme 166).[11, 12]



Scheme 166 (a) Reported asymmetric Simmons-Smith reaction and (b) potential synthesis of (1*R*,2*R*)-**213**.

4.3 REFERENCES

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CHAPTER 5 - EXPERIMENTAL

5.1 GENERAL EXPERIMENTAL

Room temperature refers to ambient temperature (20-22 °C), 5 ºC refers to a cold water bath and 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions involving moisture sensitive compounds were performed under an atmosphere of dry, oxygen free, nitrogen and in dry solvents. All commercially available solvents and chemicals were used without any further purification. pH 2 buffer is an aqueous solution (0.25 M H_2SO_4 and 0.75 M Na_2SO_4). 0.1 M phosphate buffer is an aqueous solution (0.5 M Na_2HPO_4 and 0.5 M NaH_2PO_4).

NMR spectra were recorded on Bruker Advance DRX 250, 300, 400 and 600 MHz spectrometers at room temperature (298 K). Chemical shifts are reported in parts per million (ppm) referenced from $CDCl_3$ (δ_H: 7.26 ppm and δ_C: 77.0 ppm). Coupling constants (*J*) are rounded to the nearest 0.5 Hertz (Hz). Multiplicities are given as multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sext.), septet (sept.), octet (oct.) and nonet (non.). ^{1}H and ^{13}C assignments were established on the basis of COSY, DEPT, HMQC and HMBC correlations.

Infra-red spectra were recorded using either a Perkin Elmer Spectrum 100 FT-IR spectrometer or an Alpha Bruker Platunium ATR single reflection diamond ATR module.

Optical rotations were measured using an Optical Activity Ltd AA-1000 millidegree auto-ranging polarimeter (589 nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

Melting points were recorded on a Stuart scientific melting point apparatus and are uncorrected.

Silica column chromatography was performed on 40-60 Å silica gel. Thin layer chromatography (TLC) was carried out aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. Visualisation was effected by UV light (254 nm) or by potassium permanganate solution followed by heating.

Low resolution mass spectra (LRMS) were recorded using an Agilent 6130B single Quad (ESI). High resolution mass spectra (HRMS) were obtained were obtained by either Dr Lijiang Song, Mr Philip Aston or Dr Rebecca Wills using a Bruker micro-TOF ESI spectrometer. GC-MS analysis was performed on a Varian 4000 GC/MS/MS instrument using either electron impact (EI) or chemical ionisation (CI) with helium (carrier gas) and methane (reagent gas). Elemental analyses were performed by Warwick Analytical Services.

Chiral HPLC was performed on Chiralcel OD-H or AD-H columns (Diacel Industries Ltd) using a Varian Prostar 335 Photodiode Array Detector, a Varian Prostar Solvent Delivery Module and a Varian Prostar 420 Autosampler.

Chiral GC was performed on a CP-Chirasil-Dex Cβ column (Chrompak) using either a Hewlett Packard 5890 chromatograph fitted with a flame ionisation detector linked to a Hewlett Packard HP3396A integrator or a Perkin-Elmer 8500 chromatograph fitted with a flame ionisation detector linked to a PC running DataApex Clarity software.

Single X-ray crystal structures were performed by Dr Guy J. Clarkson on an Oxford Diffraction Gemini XRD which was obtained with support from Advantage West Midlands and part funded by the European Regional Development Fund.

Acetate derivatives of trichlorocarbinols for GC injection were prepared by stirring 10 mg of the appropriate alcohol with acetic anhydride (1.5 equiv.) and pyridine (2.0 equiv.) in CH_2Cl_2 (1 mL) for 17 hours at room temperature. The reaction mixture was

concentrated *in vacuo*, filtered through a short plug of silica and washed with ethyl acetate, where it was injected directly into the GC.

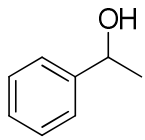
Enzyme activities are derived from the following: PLE from Sigman Aldrich, 1 unit will hydrolyse 1.0 µL of ethyl butyrate to butyric acid and ethanol per min. at pH 8.0 at 25 ºC; CRL from Sigma Aldrich, 1 unit liberates 1 µmol of fatty acid from olive oil in 1 h at pH 7.2 and 37 ºC; CRL from Fluka, 1 unit hydrolyses 1 µmol of oleic acid per min. at pH 8.0 and 40 ºC; CRL from Biocatalysts Ltd, 1 unit liberates 1 µmol of fatty acid from olive oil at pH 7.0 and 37 ºC.

5.2 EXPERIMENTAL FOR CHAPTER 1

5.2.1 Synthesis of Racemic Alcohols, 20-22. General Procedure 1:

To ketone (2 mmol, 1 equiv.) in ethanol (5 mL) was added portionwise sodium borohydride (0.91 g, 2.4 mmol, 1.2 equiv.) under ice. Reaction mixture was stirred for 20 minutes under ice and then at room temperature for 17 hours. Reaction mixture was cooled to 5 °C and quenched with water (10 mL). Ethanol was removed *in vacuo* and the resulting colourless solution was acidified with pH 2 buffer. Acidified solution was then extracted with ethyl acetate (3 x 40 mL). Organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (20 % ethyl acetate in 40-60 petroleum ether).

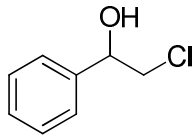
1-Phenylethanol 20.



The title compound was synthesised using General Procedure 1 with acetophenone (240 mg, 2 mmol) to give a colourless oil (115 mg, 47 %).

ν_{max}/cm^{-1} (neat) 3338 (br., OH st.), 1075 (m, C-O st.); δ_H (400 MHz; $CDCl_3$) 7.34-7.24 (5H, m, Ar*H*), 4.78 (1H, q, *J* 6.5, C*H*OH), 3.38 (1H, d, *J* 3.5, O*H*), 1.43 (3H, d, *J* 6.5, CH_3); δ_C (100 MHz; $CDCl_3$) 145.7 (Ar$C_{quat.}$), 128.1 (Ar*C*), 127.0 (Ar*C*), 125.2 (Ar*C*), 69.8 (*C*HOH), 24.9 (*C*H_3). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[1]

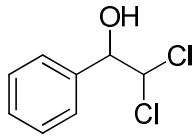
2-Chloro-1-phenylethanol 21.



The title compound was synthesised using General Procedure 1 with 2-chloroacetophenone (309 mg, 2 mmol) to give a colourless oil (256 mg, 82 %).

ν_{max}/cm^{-1} (neat) 3382 (br., OH st.), 1062 (m, C-O st.), 766 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.39-7.31 (5H, m, Ar*H*), 4.90 (1H, dd, *J* 8.5 and 3.5, C*H*OH), 3.74 (1H, dd, *J* 11 and 3.5, CH_2Cl), 3.64 (1H, dd, *J* 11 and 8.5, CH_2Cl), 2.55 (1H, br. s, O*H*); δ_C (100 MHz; $CDCl_3$) 139.9 (Ar$C_{quat.}$), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*), 73.9 (*C*HOH), 50.7 (*C*H_2Cl); GC-MS (EI) 189 (M-H); GC-MS (EI) 139.2 ($[C_8H_8{}^{35}Cl]^+$, $[M\text{-}OH]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[2]

2,2-Dichloro-1-phenylethanol 22.



The title compound was synthesised using General Procedure 1 with 2,2-dichloroacetophenone (378 mg, 2 mmol) to give a colourless oil (279 mg, 73 %).

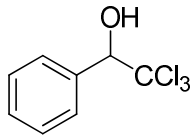
ν_{max}/cm^{-1} (neat) 3415 (br., OH st.), 1190 (m, C-O st.), 784 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.45-7.37 (5H, m, Ar*H*), 5.83 (1H, d, *J* 5.5, C*H*OH), 4.98 (1H, d, *J* 5.5, C*H*Cl_2),

3.02 (1H, br s, O*H*); δ_C (100 MHz; $CDCl_3$) 137.3 (Ar$C_{quat.}$), 129.0 (Ar*C*), 128.5 (Ar*C*), 127.1 (Ar*C*), 78.8 (*C*HOH), 76.4 (*C*H_2Cl); GC-MS (EI) 189.3 ($[C_8H_7{}^{35}Cl_2O]^+$, $[M-H]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[3]

5.2.2 Synthesis of Racemic Trichlorocarbinols. General Procedure 2:

To a solution of the appropriate aldehyde (10 mmol) in DMF (13.5 mL), cooled to 5 °C, was added trichloroacetic acid (2.45 g, 15 mmol). After stirring for 10 minutes, sodium trichloroacetate (2.78 g, 15 mmol) was added portionwise. The mixture was stirred at 5 °C for 30 minutes and then allowed warmed to room temperature where it was stirred for 17 hours. The reaction mixture was cooled to 5 °C before being quenched with water (10 mL). The reaction mixture was extracted with diethyl ether (3 x 40 mL). Organic extracts were combined and washed with sat. aq. sodium hydrogen carbonate (50 mL) and water (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residues were purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether).

2,2,2-Trichloro-1-phenylethanol 23.

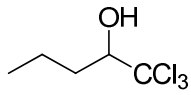


The title compound was synthesised using General Procedure 2 with benzaldehyde (1.05 mL, 10 mmol) to give a colourless oil (2.21 g, 98 %).

ν_{max}/cm^{-1} (neat) 3384 (br., OH st.), 1062 (m, C-O st.), 776 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.63 (2H, dd, *J* 7 and 1.5, Ar*H*), 7.46-7.38 (3H, m, Ar*H*), 5.21 (1H, d, *J* 3, C*H*OH), 3.51 (1H, d, *J* 3, O*H*); δ_C (100 MHz; $CDCl_3$) 134.8 (Ar$C_{quat.}$), 129.4 (Ar*C*), 129.1 (Ar*C*), 127.8 (Ar*C*), 103.0 (*C*Cl_3), 84.4 (*C*HOH); GC-MS (EI) 207.3

($[C_8H_6{}^{35}Cl_3]^+$, M-OH), 153.2 ($[C_8H_6{}^{35}ClO]^+$, $[M-{}^{37}Cl_2H]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[4]

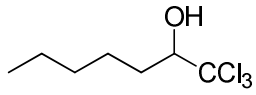
1,1,1-Trichloropentan-2-ol 40.



The title compound was synthesised using General Procedure 2 with butyraldehyde (0.72 g, 10 mmol) to give a colourless oil (1.61 g, 84 %).

ν_{max}/cm^{-1} (neat) 3338 (br., OH st.), 1078 (m, C-O st.), 772 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.02 (1H, dd, *J* 9.5 and 2, C*H*OH), 2.66 (1H, br. s, O*H*), 2.06-1.97 (1H, m, CH_2), 1.75-1.59 (2H, m, CH_2), 1.55-1.42 (1H, m, CH_2), 1.00 (3H, t, *J* 7, CH_3); δ_C (100 MHz; $CDCl_3$) 104.3 (*C*Cl_3), 82.7 (*C*HOH), 33.5 (*C*H_2COH), 19.4 (*C*H_2CH_3), 13.8 (*C*H_3); GC-MS (EI) 137.1 ($[C_5H_7{}^{35}Cl_2]^+$, $[M-{}^{37}ClH_2O]^+$); Anal. for $C_5H_9Cl_3O$, Calcd: C, 31.36; H, 4.74. Found: C, 31.75; H, 4.82. It was not possible to obtain a HRMS (ESI) of this compound. This compound is known but has previously only been reported with ^{1}H NMR data, which are consistent with that reported here.[5]

1,1,1-Trichloroheptan-2-ol 24.

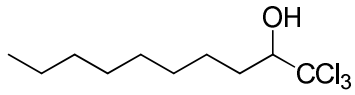


The title compound was synthesised using General Procedure 2 with hexanal (1.2 mL, 10 mmol) to give a colourless oil (1.71 g, 78 %).

ν_{max}/cm^{-1} (neat) 3395 (br., OH st.), 1088 (m, C-O st.), 780 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.00 (1H, d, *J* 9.5, C*H*OH), 2.79 (1H, br. s, O*H*), 2.08-2.00 (1H, m, CH_2), 1.70-1.58 (2H, m, CH_2), 1.53-1.42 (1H, m, CH_2), 1.39-1.30 (4H, m, CH_2), 0.91 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 104.4 (*C*Cl_3), 83.0 (*C*HOH), 31.5 (*C*H_2), 31.4 (*C*H_2), 25.7

(CH_2), 22.5 (CH_2CH_3), 14.0 (CH_3). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[6]

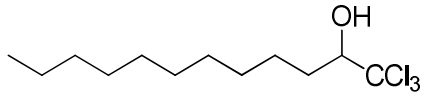
1,1,1-Trichlorodecan-2-ol 41.



The title compound was synthesised using General Procedure 2 with nonanal (1.42 g, 10 mmol) to give a colourless oil (2.49 g, 95 %).

ν_{max}/cm^{-1} (neat) 3402 (br., OH st.), 1086 (m, C-O st.), 780 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.00 (1H, dd, *J* 9.5 and 2.0, C*H*OH), 2.70 (1H, br. s, O*H*), 2.09-1.99 (1H, m, C*H*$_2$), 1.68-1.58 (2H, m, C*H*$_2$), 1.39-1.22 (11H, m, C*H*$_2$), 0.88 (3H, t, *J* 6.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 104.4 (*C*Cl_3), 83.0 (*C*HOH), 31.8 (*C*H_2), 31.5 (*C*H_2), 29.4 (*C*H_2), 29.3 (*C*H_2), 29.2 (*C*H_2), 26.1 (*C*H_2), 22.6 (*C*H_2), 14.1 (*C*H_3); GC-MS (EI) 225.4 ($[C_{10}H_{19}{}^{35}Cl_2O]^+$, $[M-{}^{37}Cl]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[7]

1,1,1-Trichlorododecan-2-ol 42.

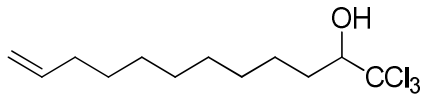


The title compound was synthesised using General Procedure 2 with undecanal (1.70 g, 10 mmol) to give a yellow oil (2.72 g, 94 % yield).

ν_{max}/cm^{-1} (neat) 3329 (br., OH st.), 1075 (m, C-O st.), 760 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.00 (1H, dd, *J* 9.5, 2 C*H*OH), 2.73 (1H, br. s, O*H*), 2.09-2.00 (1H, m, C*H*$_2$COH), 1.70-1.58 (2H, m, C*H*$_2$COH and C*H*$_2$CH$_2$COH), 1.50-1.40 (1H, m, C*H*$_2$CH$_2$COH), 1.41-1.23 (14H, m, C*H*$_2$), 0.88 (3H, t, *J* 7, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 104.4 (*C*Cl_3), 83.0 (*C*HOH), 31.9, 31.5, 29.6, 29.4, 29.3, 26.1, 22.7 (7 x *C*H_2), 14.1 (*C*H_3); GC-MS (CI) 287.4 ($[C_{12}H_{22}{}^{35}Cl_3O]^+$, $[M-H]^+$), 253.3 ($[C_{12}H_{23}{}^{35}Cl_2O]^+$, $[M-{}^{37}Cl]^+$); Anal. for $C_{12}H_{23}Cl_3O$, Calcd: C, 49.76; H, 8.00. Found: C, 50.49; H, 8.43. Two

of the *C*H_2 peaks in the ^{13}C NMR spectrum were not resolvable. It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[8]

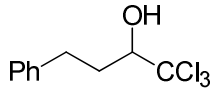
1,1,1-Trichlorododec-9-en-2-ol 43.



The title compound was synthesised using General Procedure 2 with 10-undecenal (1.68 g, 10 mmol) to give a yellow oil (1.44 g, 50 %).

ν_{max}/cm^{-1} (neat) 3445 (br., OH st.), 2925 (s, H-C(C=C) st.), 1640 (w, C=C st.), 1463 (w, H_2C(C=C) st.), 780 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.81 (1H, ddt, *J* 13.5, 10 and 6.5, C*H*=CH_2), 5.00 (1H, dq, *J* 17 and 1.5, *H*HC=CHCH_2), 4.94 (1H, ddt, *J* 10, 2 and 1, H*H*C=CHCH_2), 4.00 (1H, 9.5, 4.5 and 2, C*H*OH), 2.67 (1H, dd, 5.5 and 1.5, O*H*), 2.08-2.01 (4H, m, CH_2CH=CH_2 and CH_2OH), 1.69-1.58 (2H, m, CH_2CH_2OH), 1.41-1.30 (10H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 139.2 (*C*H=CH_2), 114.2 (*C*H_2=CH), 100.0 (*C*Cl_3), 83.0 (*C*HOH), 33.8, 31.5, 29.4, 29.3, 29.1, 28.9, 26.1 (7 x CH_2); GC-MS (EI) 250.3 ([$C_{12}H_{20}{}^{35}ClO]^+$, [M-$^{37}ClH]^+$), 232.9 ([$C_{12}H_{19}{}^{35}Cl_2]^+$, [M-$^{37}ClH_2O]^+$), 215.3 ([$C_{12}H_{20}{}^{35}ClO]^+$, [M-$^{37}Cl_2H]^+$), 199.3 ([$C_{12}H_{20}{}^{35}Cl]^+$, [M-$^{37}Cl_2OH]^+$). One *C*$H_2$ peak in the ^{13}C NMR spectrum was not resolvable. It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichloro-4-phenylbutan-2-ol 25.

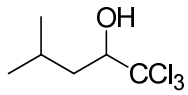


The title compound was synthesised using General Procedure 2 with 3-phenylpropionaldehyde (1.34 g, 10 mmol) to give a colourless oil (2.01 g, 80 %).

ν_{max}/cm^{-1} (neat) 3402 (br., OH st.), 1077 (m, C-O st.), 784 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.34-7.30 (2H, m, Ar*H*), 7.26-7.21 (3H, m, Ar*H*), 3.99 (1H, d, *J* 10, C*H*OH),

3.01 (1H, ddd, 14, 9 and 5, C*H*$_2$Ph), 2.84 (1H, br. s, O*H*), 2.78 (1H, dt, *J* 14 and 8.5, C*H*$_2$Ph), 2.44-2.36 (1H, m, C*H*$_2$CHOH), 2.00 (1H, m, C*H*$_2$CHOH); δ_C (100 MHz; $CDCl_3$) 140.7 (Ar-$C_{quat.}$), 128.6 (Ar*C*), 128.5 (Ar*C*), 126.2 (Ar*C*), 104.1 (*C*Cl_3), 82.0 (*C*HOH), 32.9 (*C*H_2Ph), 32.0 (*C*H_2CHOH); GC-MS (EI) 216.3 ($[C_{10}H_{10}{}^{35}Cl_2O]^+$, [M-^{37}ClH]$^+$), 181.4 ($[C_{10}H_{10}{}^{35}ClO]^+$, [M-$^{37}Cl_2H]^+$), 199.4 ($[C_{10}H_9ClO]^+$, [M-$^{37}Cl_2H_2O]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[9]

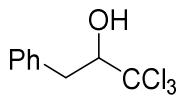
1,1,1-Trichloro-4-methylpentan-2-ol 44.



The title compound was synthesised using General Procedure 2 with 3-methylbutanal (1.04 mL, 10 mmol) to give a colourless oil (1.85 g, 90 %).

ν_{max}/cm^{-1} (neat) 3368 (br., OH st.), 1086 (m, C-O st.), 764 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.06 (1H, dd, *J* 9.5 and 1.5, C*H*OH), 2.76 (1H, br. s, O*H*), 1.92 (1H, m, C*H*), 1.77 (ddd, *J* 14, 10 and 2, C*H*HCOH), 1.63 (1H, ddd, *J* 14 , 9.5 and 4, CH*H*COH), 1.00 (d, *J* 6.5, C*H*$_3$), 0.96 (3H, d, *J* 6.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 104.6 (*C*Cl_3), 81.4 (*C*HOH), 40.3 (*C*H_2), 25.0 (*C*H), 23.6 (*C*H_3), 21.4 (*C*H_3); GC-MS (EI) 151.3 ($[C_6H_9{}^{35}Cl_2]^+$, [M-^{37}ClH_2O]$^+$). It was not possible to obtain a HRMS (ESI) of this compound. This compound is known but has previously only been reported with ^{1}H NMR data, which are consistent with that reported here.[10]

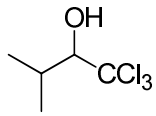
1,1,1-Trichloro-3-phenylpropan-2-ol 45.



The title compound was synthesised using General Procedure 2 with phenylacetaldehyde (1.20 g) to give a colourless oil (1.65 g, 69 %).

ν_{max}/cm^{-1} (thin film) 3401 (br., OH), 2995 (w, Ar-H), 1430 (m, C-O), 789 (C-Cl); δ_H (400 MHz; $CDCl_3$) 7.39-7.28 (5H, m, Ar*H*), 4.27 (1H, dd, *J* 10 and 2, C*H*OH), 3.46 (1H, dd, *J* 14 and 3, CH_2Ph), 2.92 (1H, dd, *J* 14 and 10, CH_2Ph), 2.84 (1H, br. s, O*H*); δ_C (100 MHz; $CDCl_3$) 137.0 (Ar-$C_{quat.}$), 129.5 (Ar*C*), 129.7 (Ar*C*), 127.0 (Ar*C*), 103.5 (*C*Cl_3), 84.0 (*C*HOH), 38.0 (*C*H_2Ph); GC-MS (EI) 238.0 ([$C_9H_9{}^{35}Cl_3O$]$^+$, M$^+$), 185.2 ([$C_9H_7{}^{35}Cl_2$]$^+$, [M-$^{37}ClH_2O$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

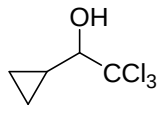
1,1,1-Trichloro-3-methylbutan-2-ol 46.



The title compound was synthesised using General Procedure 2 with 2-methylpropanal (0.91 mL, 10 mmol) to give a colourless oil (1.66 g, 87 %).

ν_{max}/cm^{-1} (neat) 3540 (br., OH st.), 1078 (m, C-O st.), 772 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.94 (1H, d, *J* 2.5, C*H*OH), 2.71 (1H, br. s, O*H*), 2.44 (1H, sept. d, *J* 7.0 and 2.5, C*H*), 1.14 (3H, d, *J* 7, CH_3), 1.09 (3H, d, *J* 7, CH_3); δ_C (100 MHz; $CDCl_3$) 104.1 (*C*Cl_3), 86.2 (*C*HOH), 30.0 (*C*H), 22.8 (*C*H_3), 16.1 (*C*H_3); GC-MS (EI) 155.1 ([$C_5H_9{}^{35}Cl_2O$]$^+$, [M-^{37}Cl]$^+$), 137.0 ([$C_5H_7{}^{35}Cl_2$]$^+$, [M-$^{37}ClH_2O$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound. This compound is known but has previously only been reported with ^{1}H NMR data, which are consistent with that reported here.[4]

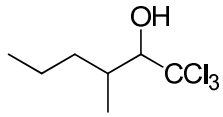
1,1,1-Trichlorocyclopropylethan-2-ol 47.



The title compound was synthesised using cyclopropanecarboxaldehyde (1.89 g, 10 mmol) to give a colourless oil (1.09 g, 57 %).

ν_{max}/cm^{-1} (neat) 3414 (br., OH st.), 1051 (m, C-O st.), 776 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.58 (1H, d, *J* 7, C*H*OH), 2.69 (1H, br. s, O*H*), 1.34-1.23 (1H, m, C*H*COH), 0.82-0.72 (1H, m, CH_2), 0.69-0.56 (3H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 103.9 (*C*Cl_3), 85.4 (*C*HOH), 12.9 (*C*HCOH), 5.2 (*C*H_2), 2.0 (*C*H_2); GC-MS (EI) 159.1 ($[C_3H_2{}^{35}Cl_3O]^+$, $[M\text{-}C_2H_5]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[10]

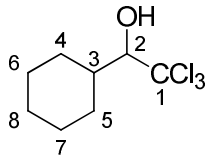
1,1,1-Trichloro-3-methylhexan-2-ol 48.



The title compound was synthesised using General Procedure 2 with 2-methyhexanal (1.00 g, 10 mmol) to give colourless oil (1.46 g, 67 %) as a 65 : 35 (a : b) mixture of diastereomers.

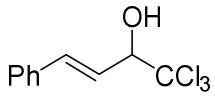
ν_{max}/cm^{-1} (neat) 3412 (br., OH st.), 1249 (s, C-O st.), 780 (s, C-Cl st.); **a**: δ_H (400 MHz; $CDCl_3$) 4.02 (1H, d, *J* 1.5, C*H*OH), 2.74 (1H, br. s, O*H*), 2.35 (1H, sext. d, *J* 7 and 1.5, C*H*CH_3), 1.46-1.38 (3H, m, CH_2C*H*HCH_3), 1.35-1.22 (1H, m, C$H_2$$CH_3$), 1.11 (3H, d, *J* 7, CHCH_3), 0.96 (3H, t, *J* 7, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 104.3 (*C*Cl_3), 84.9 (*C*HOH), 39.0 (*C*H_2CH_3), 34.1 (*C*HCH_3), 20.0 (*C*H_2CH_3), 14.0 (*C*H_3CH_2), 13.5 (*C*H_3CH); **b**: δ_H (400 MHz; $CDCl_3$) 3.94 (1H, d, *J* 3, C*H*OH), 2.74 (1H, br. s, O*H*), 2.24 (1H, sext. d, *J* 7 and 3, C*H*CH_3), 1.90-1.81 (1H, m, C$H_2$$CH_3$), 1.57-1.48 (2H, m, C$H_2CH_2CH_3$), 1.46-1.38 (1H, m, C$H_2$$CH_3$), 1.17 (3H, d, *J* 7, CHCH_3), 0.95 (3H, t, *J* 7, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 104.4 (*C*Cl_3), 86.7 (*C*HOH), 35.0 (*C*HCH_3), 32.4 (*C*H_2CH_3), 21.1 (*C*H_3CH_2), 20.4 (*C*H_2CH_3), 19.6 (*C*H_3CH); Anal. for $C_7H_{13}Cl_3O$, calc.: C, 38.30; H, 5.97. Found: C, 38.26; H, 6.01. It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichlorocyclohexylethan-2-ol 26.



The title compound was synthesised using General Procedure 2 with cyclohexanecarboxaldehyde (1.12 g, 10 mmol) to give a colourless oil (1.90 g, 82 %). ν_{max}/cm^{-1} (neat) 3447 (br., OH st.), 2925 (s, cyclohexane C-H st.), 2853 (m, cyclohexane C-H st.), 1449 (w, cyclohexane C-H bend), 1109 (m, C-O st.), 762 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.86 (1H, d, *J* 2, C*H*OH), 2.80 (1H, br. s, O*H*), 2.10-2.00 (2H, m, C*H*C*H*$_2$), 1.78-1.63 (4H, m, C*H*$_2$), 1.48-1.00 (5H, m, C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 104.2 (*C*Cl_3), 86.4 (*C2*), 39.9 (*C3*), 32.9 (*C8*), 26.7 (*C*H_2), 26.5 (*C*H_2), 26.0 (*C*H_2), 25.9 (*C*H_2); GC-MS (EI) 195.3 ([$C_8H_{13}{}^{35}Cl_2O$]$^+$, [M-^{37}Cl]$^+$), 177.2 ([$C_8H_{11}{}^{35}Cl_2$]$^+$, [M-$^{37}ClH_2O$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[4, 11]

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol (*E*)-49.



The title compound was synthesised using general method 2 with *trans*-cinnamaldehyde (1.32 g, 10 mmol) to give a light orange solid (1.17 g, 47 %).

m.p. 64-65 ºC; ν_{max}/cm-1 (neat) 3284 (br, OH), 1047 (m, C-O), 784 (C-Cl); δ_H (400 MHz; $CDCl_3$) 7.47-7.41 (2H, m, Ar*H*), 7.38-7.27 (3H, m, Ar*H*), 6.89 (1H, d, *J* 16, PhC*H*=CH), 6.37 (1H, ddd, *J* 16, 6 and 1, =C*H*COH), 4.76 (1H, d, *J* 6, C*H*OH), 3.16 (1H, br. s, O*H*); δ_C (100 MHz; $CDCl_3$) 136.7 (=*C*HPh), 135.6 (Ar$C_{quat.}$), 128.7 (Ar*C*), 128.6 (Ar*C*), 126.9 (Ar*C*), 122.6 (=*C*HCOH), 102.8 (*C*Cl_3), 83.3 (*C*HOH); HRMS (ESI) calc. for $C_{10}H_9{}^{35}Cl_3NaO$ (M+Na$^+$) 272.9611, found 272.9613. These data are consistent with that previously reported.[12]

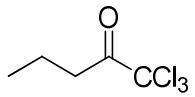
5.2.3 Oxidation of Racemic Trichlorocarbinols with Sodium Dichromate.

General Procedure 3:

Method modified from the literature.[13]

To a solution of the appropriate trichlorocarbinol (10 mmol) in acetic acid (20 mL), cooled to 5 °C, was added dropwise a solution of $NaCr_2O_7.2H_2O$ (3.58 g, 12 mmol) and concentrated sulfuric acid (1.07 mL, 20 mmol) in glacial acetic acid (20 mL). The mixture was stirred at 5 °C for 15 minutes before being allowed to warm to room temperature and stirred for 17 hours. The excess oxidant was destroyed by the addition of 2-propanol (1.5 mL) and resulting solution was stirred at room temperature for 10 minutes. To the reaction mixture was added sat. aq. ammonium chloride (50 mL) which was extracted with dichloromethane (2 x 40 mL). The organic layers were combined and washed with 5 % aq. sodium hydrogen carbonate (4 x 40 mL), sat. aq. sodium hydrogen carbonate (50 mL) and then water (50 mL). Organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography (95 : 5 40-60 petroleum ether : ethyl acetate).

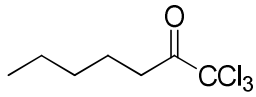
1,1,1-Trichloropentan-2-one 50.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichloropentan-2-ol **40** (0.73 g, 3.8 mmol) to give a colourless oil (0.37 g, 50 % yield). ν_{max}/cm^{-1} (neat) 1759 (s, C=O st.), 778 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.97 (2H, t, *J* 7, C*H*$_2$CO), 1.78 (2H, sext., *J* 7.5, C*H*$_2$CH$_3$), 1.00 (3H, t, *J* 7.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 190.5 (*C*O), 96.5 (*C*Cl$_3$), 35.7 (*C*H$_2$CO), 18.3 (*C*H$_2$CH$_3$), 13.3 (*C*H$_3$); GC-MS (EI) 172.2 ($[C_5H_7{}^{35}Cl_3]^+$, $[M\text{-}CO]^+$). It was not possible to obtain a HRMS (ESI) of this

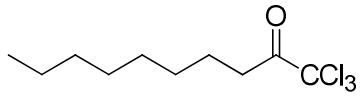
compound. This compound is known but has previously only been reported with ^{1}H NMR data, which are consistent with that reported here.[14]

1,1,1-Trichloroheptan-2-one 51.



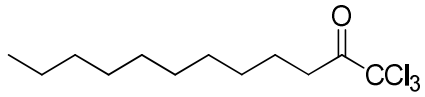
The title compound was synthesised using General Procedure 3 with 1,1,1-trichloroheptan-2-ol **24** (2.19 g, 10 mmol) to give a colourless oil (1.76 g, 80 % yield). ν_{max}/cm^{-1} (neat) 1753 (s, C=O st.), 747 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.99 (2H, t, *J* 7.5, C*H*$_2$CO), 1.74 (2H, quin., *J* 7.5, C*H*$_2$CH$_2$CO), 1.37-1.29 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.90 (3H, t, *J* 7, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 190.6 (*C*O), 96.5 (*C*Cl$_3$), 33.8 (*C*H$_2$CO), 30.9 (*C*H$_2$), 24.5 (*C*H$_2$), 22.3 (*C*H$_2$), 13.8 (*C*H$_3$).

1,1,1-Trichlorodecan-2-one 52.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichlorodecan-2-ol **41** (1.96 g, 7.5 mmol) to give a colourless oil (1.34 g, 68 %). ν_{max}/cm^{-1} (neat) 1755 (s, C=O st.), 745 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.97 (2H, t, *J* 7.5, C*H*$_2$CO), 1.74 (2H, quin., *J* 7, C*H*$_2$CH$_2$CO), 1.40-1.27 (12H, m, 6 x C*H*$_2$), 0.88 (3H, t, *J* 6.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 190.6 (*C*O), 96.5 (*C*Cl$_3$), 33.9 (*C*H$_2$CO), 31.8 (*C*H$_2$), 29.2 (*C*H$_2$), 29.0 (*C*H$_2$), 28.8 (*C*H$_2$), 22.6 (*C*H$_2$), 14.1 (*C*H$_3$). It was not possible to obtain a HRMS (ESI) of this compound.

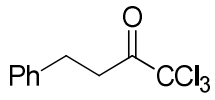
1,1,1-Trichlorodecan-2-one 53.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichlorodecan-2-ol (**63**) (2.88 g, 10 mmol) to give a colourless oil (1.58 g, 55 %).

ν_{max}/cm^{-1} (neat) 1754 (s, C=O st.), 746 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.97 (2H, t, *J* 7.5, C*H*$_2$CO), 1.74 (2H, pent., *J* 7, C*H*$_2$), 1.45-1.22 (14H, m, 7 x C*H*$_2$), 0.88 (3H, t, *J* 7, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 190.7 (*C*O), 96.4 (*C*Cl_3), 33.9 (*C*H_2CO), 31.9 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2), 29.3 (*C*H_2), 29.2 (*C*H_2), 28.8 (*C*H_2), 24.8 (C*H*$_2$CH$_2$CO), 22.7 (*C*H_2), 14.1 (*C*H_3); GC-MS (CI) 287.3 ([$C_{12}H_{22}{}^{35}Cl_3O$]$^+$, [M+H]$^+$), 251.4 ([$C_{12}H_{21}{}^{35}Cl_2O$]$^+$, [M-^{37}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

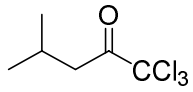
1,1,1-Trichloro-4-phenyl-2-butanone 54.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichloro-4-phenyl-2-butanol **25** (2.52 g, 10 mmol) to give a colourless oil (2.28 g, 90 %).

ν_{max}/cm^{-1} (neat) 1749 (s, CO st.), 741 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.37-7.33 (3H, m, Ar*H*), 7.28-7.25 (2H, m, *o*-Ar*H*), 3.35 (2H, t, *J* 8.0, C*H*$_2$CO), 3.10 (2H, t, *J* 7.5, C*H*$_2$Ph); δ_C (100 MHz; $CDCl_3$) 189.6 (*C*O), 139.5 (Ar*C*$_{quat.}$), 128.6 (Ar*C*), 128.4 (Ar*C*), 126.6 (Ar*C*) 96.2 (*C*Cl_3), 35.8 (*C*H_2COCCl_3), 30.8 (*C*H_2Ph). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[15]

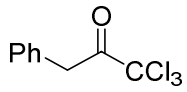
1,1,1-Trichloro-4-methylpentan-2-one 55.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichloro-4-methylpentan-2-ol **44** (2.05 g, 10 mmol) to give a colourless oil (1.82 g, 89 %).

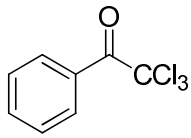
ν_{max}/cm^{-1} (neat) 1752 (s, C=O st.), 774 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.85 (2H, d, *J* 7, C*H*$_2$), 2.27 (1H, non., *J* 7, C*H*), 0.99 (6H, d, *J* 7, 2 x C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 189.6 (*C*O), 96.6 (*C*Cl_3), 42.5 (*C*H_2), 25.2 (*C*H), 22.1 (2 x *C*H_3). It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichloro-3-phenylpropan-2-one 56.



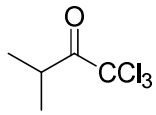
The title compound was synthesised using General Procedure 3 with 1,1,1-trichloro-3-phenylpropan-2-ol **45** (0.516 g, 2.2 mmol) to give a colourless oil (0.433 g, 84 %). ν_{max}/cm^{-1} (neat) 1754 (s, C=O st.), 749 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.41-7.33 (5H, m, Ar*H*), 4.29 (1H, s, C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 187.7 (*C*O), 132.8 (Ar*C*$_{quat.}$), 129.4 (Ar*C*), 128.7 (Ar*C*), 127.5 (Ar*C*), 96.4 (*C*Cl_3), 41.4 (*C*H_2); GC-MS (EI) 185.5 ([$C_9H_7{}^{35}Cl_2$]$^+$, M-^{35}ClO), 149.5 ([$C_9H_7{}^{35}Cl$]$^+$, [M-$^{37}Cl_2O$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichlorophenylethan-2-one 57.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichlorophenylethan-2-ol **23** (2.25 g, 10 mmol) to give a colourless oil (1.56 g, 70 %). ν_{max}/cm^{-1} (neat) 1709 (s, C=O st.), 820 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 8.24 (2H, d, *J* 7.5, *o*-Ar*H*), 7.60 (1H, t, *J* 6.5, *p*-Ar*H*), 7.47 (2H, t, *J* 7, *m*-Ar*H*); δ_C (100 MHz; $CDCl_3$) 180.8 (*C*=O), 134.1 (Ar*C*), 131.2 (Ar*C*), 128.8 (Ar*C*$_{quat.}$), 128.2 (Ar*C*), 95.3 (*C*Cl_3); GC-MS (EI) 187.1 ([$C_8H_5{}^{35}Cl_2O$]$^+$, M-^{35}Cl), 159.2 ([$C_7H_5{}^{35}Cl_2$]$^+$, [M-^{37}ClCO]$^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[13]

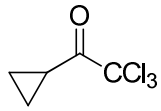
1,1,1-Trichloro-3-methylbutan-2-one 58.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichloro-3-methylbutan-2-ol **46** (1.07 g, 5.6 mmol) to give a colourless oil (0.84 g, 79 %).

ν_{max}/cm^{-1} (neat) 1732 (s, C=O st.), 740 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.53 (1H, sept., *J* 6.5, C*H*), 1.33 (6H, d, *J* 6.5, 2 x CH_3); δ_C (100 MHz; $CDCl_3$) 194.6 (*C*O), 96.5 (*C*Cl_3), 34.0 (*C*H), 21.4 (2 x *C*H_3). This compound is known but has previously only been reported with ^{1}H NMR data, which are consistent with that reported here.[16]

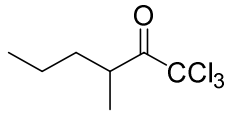
1,1,1-Trichlorocyclopropylethan-2-one 59.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichlorocyclopropylethan-2-ol **47** (2.01 g, 10.6 mmol) to afford a colourless oil (1.73 g, 87 %).

ν_{max}/cm^{-1} (neat) 3016 (w, cyclopropane C-H), 1732 (s, C=O st.), 787 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 2.58 (1H, tt, *J* 8 and 5, C*H*CO), 1.22-1.16 (4H, m, 2 x C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 191.3 (*C*O), 100.7 (*C*Cl_3), 15.0 (*C*HCO), 14.0 (*C*H_2); GC-MS (EI) 151.1 ([$C_5H_5{}^{35}Cl_2O$]$^+$, [M-^{37}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

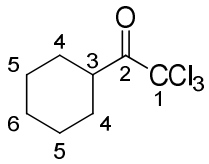
1,1,1-Trichloro-3-methylhexan-2-one 60.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichloro-3-methylhexan-2-ol **48** (0.728 g, 3.3 mmol) to give a colourless oil (0.365 g, 50 %).

ν_{max}/cm^{-1} (neat) 1754 (s, C=O st.), 749 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.39 (1H, sext., *J* 7.0, C*H*CH_3), 1.72 (1H, dtd, *J* 13.5, 10.5 and 6.5, C*H*HCOH), 1.41-1.20 (3H, m, CH*H*COH and C*H*$_2$$CH_3$), 1.25 (3H, d, *J* 7, CHC*H*$_3$), 0.86 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 194.1 (*C*O), 96.7 (*C*Cl_3), 39.0 (*C*HCH_3), 37.4 (*C*$H_2CH_2CH_3$), 20.5 (*C*H_2CH_3), 19.7 (CH*C*H_3), 14.0 (CH_2*C*H_3). It was not possible to obtain a HRMS (ESI) of this compound.

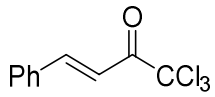
1,1,1-Trichlorocyclohexylethan-2-one 61.



The title compound was synthesised using General Procedure 3 with 1,1,1-trichlorocyclohexylethan-2-ol **26** (0.69 g, 3 mmol) to afford a white solid (0.54 g, 78 %).

m.p. 43-45 °C; ν_{max}/cm^{-1} (neat) 2929 (s, cyclohexane C-H st.), 2856 (m, cyclohexane C-H st.), 1736 (s, C=O st.), 1453 (w, cyclohexane C-H bend), 710 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 3.24 (1H, tt, *J* 11.5 and 3.5, C*H*CO), 2.03-1.94 (2H, m, C*H*$_2$CHC*H*$_2$), 1.84 (2H, dq, *J* 13.5 and 3.5, C*H*$_2$), 1.77-1.70 (1H, m, C*H*$_2$), 1.60 (2H, qd, *J* 12.5 and 3, C*H*$_2$CHC*H*$_2$), 1.41-1.24 (3H, m, C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 193.1 (*C*O), 96.7 (*C*Cl_3), 44.0 (*C3*), 31.3 (*C4*), 25.4 (*C*H_2), 25.3 (*C*H_2); GC-MS (EI) 193.2 ([$C_8H_{11}{}^{35}Cl_2O$]$^+$, [M-^{37}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

5.2.4 Synthesis of 1,1,1-Trichloro-4-phenylbut-3-en-2-one (*E*)-62.

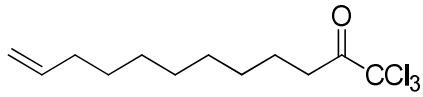


Method modified from the literature.[17]

To a solution of 1,1,1-trichloro-4-phenylbut-3-en-2-ol (*E*)-**49** (3.77 g, 15.1 mmol) in CH_2Cl_2 (150 mL) was added MnO_2 (19.13 g, 225 mmol, 15 equiv.). The reaction mixture was stirred at room temperature for 72 h. The residue was filtered through Celite®, concentrated *in vacuo* and purified by silica column chromatography (*n*-hexane) to give a beige solid (3.10 g, 81 %).

ν_{max}/cm^{-1} (neat) 1706 (s, C=O st.), 1604 (s, C=C st.), 741 (C-Cl); δ_H (400 MHz; $CDCl_3$) 8.01 (1H, d, *J* 15.5, =C*H*Ph), 7.68-7.64 (2H, m, Ar*H*), 7.51-7.42 (3H, m, Ar*H*), 7.35 (1H, d, *J* 15.5, =C*H*CO); δ_C (100 MHz; $CDCl_3$) 180.0 (*C*O), 149.6 (=*C*HPh), 133.7 (Ar$C_{quat.}$), 131.7 (Ar*C*), 129.1 (Ar*C*), 129.0 (Ar*C*), 115.8 (=C*H*CO), 96.4 (*C*Cl_3); GC-MS (CI) 249.4 ($C_{10}H_8{}^{35}Cl_3O]^+$, $[M+H]^+$). It was not possible to obtain a HRMS (ESI) of this compound. These data are consistent with that previously reported.[18]

5.2.5 Synthesis of 1,1,1-Trichlorodec-9-en-2-one 63.



Method modified from the literature.[19]

To a solution of 1,1,1-trichlorodec-9-en-2-ol **43** (2.2 g, 7.7 mmol) in dry ethyl acetate (60 mL) was added at once 2-iodoxybenzoic acid (6.44g, 23.1 mmol). The suspension was heated under reflux for 24 h under nitrogen. The reaction mixture was allowed to cool to room temperature. The resulting suspension was filtered through Celite®, concentrated *in vacuo* and purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (1.22 g, 55 %).

ν_{max}/cm^{-1} (neat) 2926 (s, H-C=C st.), 1754 (s, C=O st.), 747 (C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.81 (1H, ddt, *J* 17, 10 and 6.5, C*H*=CH_2), 4.97 (2H, m, CH_2=CH), 2.97 (2H, t, *J* 7, CH_2CO), 2.04 (2H, m, CH_2CH=CH_2), 1.74 (2H, quin., *J* 7.5, CH_2CH_2CO), 1.42-1.30 (10H, m, 5 x CH_2); δ_C (100 MHz; $CDCl_3$) 190.7 (*C*O), 139.2 (*C*H=CH_2), 114.2 (CH=*C*H_2), 102.7 (*C*Cl_3), 33.9 (*C*H_2CHC=CH_2), 33.8 (*C*H_2CO), 29.3 (*C*H_2), 29.2 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 28.8 (*C*H_2), 24.8 (*C*H_2CH_2CO); GC-MS (CI) 285.3 ($[C_{12}H_{20}{}^{35}Cl_3O]^+$, $[M+H]^+$), 249.4 ($[C_{12}H_{19}{}^{35}Cl_2O]^+$, M-^{37}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

5.2.6 ATH of Trichloroketones using Ruthenium Dimers. General Procedure 4:

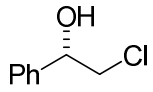
Arene-ruthenium dichloride dimer (2.5 x 10^{-3} mmol) and ligand (5.0 x 10^{-3} mmol) were stirred in formic acid/triethylamine (5 : 2) azeotrope (0.5 mL) at 28 °C under nitrogen for 30 minutes. To this was added the appropriate ketone (1 mmol), dissolved in dry ethyl acetate (0.5 mL) if required, and resulting solution was stirred at 28 °C under nitrogen for 17 hours unless otherwise stated. Reaction mixture was purified immediately by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether).

5.2.7 ATH of Trichloroketones using (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-17. General Procedure 5:

(*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (5.0 x 10^{-3} mmol) was stirred in formic acid/triethylamine (5 : 2) azeotrope (0.5 mL) at 28 °C under nitrogen for 30 minutes. To this solution was added the appropriate ketone (1 mmol) and resulting solution was stirred at 28 °C under nitrogen for a given time. Reaction mixture was purified

immediately by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether).

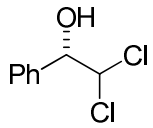
(*S*)-2-Chloro-1-phenylethanol (*S*)-21.



The title compound was synthesised using General Procedure 4 with chloroacetophenone (155 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (121 mg, 77 %, 94 % e.e.).

Spectroscopic data similar to racemate; $[\alpha]_D^{29}$ (*c* 1.3, C_6H_{12}): + 42.6 (*S*) lit.[20, 21]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 3 : 97, 1 mL/min., 210 nm, (*S*)-isomer 20.23 min., (*R*)-isomer 23.70 min.).

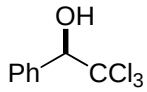
(*S*)-2,2-Dichloro-1-phenylethanol (*S*)-22.



The title compound was synthesised using General Procedure 4 with 2,2-dichloroacetophenone (189 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (132 mg, 69 %, 64 % e.e.).

Spectroscopic data similar to racemate; $[\alpha]_D^{29}$ (*c* 1.8, CH_2Cl_2): + 17.8 (*S*) lit.[22]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 4 : 96, 1 mL/min., 209 nm, (*R*)-isomer 21.12 min., (*S*)-isomer 22.35 min.).

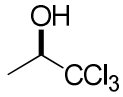
(*R*)-2,2,2-Trichloro-1-phenylethanol (*R*)-23.



The title compound was synthesised using General Procedure 4 with 2,2,2-trichloroacetophenone **57** (224 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (187 mg, 83 %, 29 % e.e.).

Spectroscopic data similar to racemate; $[\alpha]_D^{26}$ (c 0.94, $CHCl_3$): - 10.9 (*R*) lit.[13, 22]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 228 nm, (*R*) isomer-14.83 min., (*S*)-isomer 21.92 min.).

(*R*)-1,1,1-Trichloropropan-2-ol (*R*)-65.



The title compound was synthesised using General Procedure 4 with 2,2,2-trichloroacetone (645 g, 4 mmol), [Ru(benzene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (359 mg, 55 %, 84 % e.e.).

$[\alpha]_D^{23}$ (*c* 1.16, $CHCl_3$): +4.8 (*R*) lit.[22]; ν_{max}/cm^{-1} (neat) 3332 (br., OH st.), 1160 (m, C-O st.), 791 (C-Cl); δ_H (400 MHz; $CDCl_3$) 4.28 (1H, q, *J* 6, C*H*OH), 2.75 (1H, br. s, O*H*), 1.52 (1H, d, *J* 6, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 104.5 (*C*Cl_3), 79.2 (*C*HOH), 17.7 (*C*H_3). Enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 60 °C, P = 15 psi (H_2 gas), (*S*)-isomer 59.8 min., (*R*)-isomer 64.3 min.).

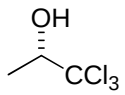
The title compound was synthesised using General Procedure 4 with 2,2,2-trichloroacetone (2.40 g, 15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (2.07 g, 85 %, 98 % e.e.).

Spectroscopic data similar to that previously reported; Enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 60 °C, P = 15 psi (H_2 gas), (*S*)-isomer 67.1 min., (*R*)-isomer 71.3 min.).

The title compound was synthesised using General Procedure 5 with 2,2,2-trichloroacetone (1.13 mL, 10 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (31 mg) for 2.5 h to give a colourless oil (1.35 g, 83 %, 98 % e.e.).

Spectroscopic data similar to that previously reported. Enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 60 °C, P = 15 psi (H_2 gas), (*S*)-isomer 67.1 min., (*R*)-isomer 71.3 min.).

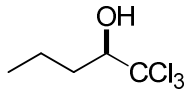
(*S*)-1,1,1-Trichloropropan-2-ol (*S*)-65.



The title compound was synthesised using General Procedure 4 with 2,2,2-trichloroacetone (645 mg, 4 mmol), [Ru(benzene)Cl_2]$_2$ and (*S*,*S*)-TsDPEN to give a colourless oil (325 mg, 50 %, 84 % e.e.).

Spectroscopic data similar to that previously reported; $[\alpha]_D^{23}$ (*c* 1.08, $CHCl_3$): - 3.8 (*S*) lit.[22]; enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 60 °C, P = 15 psi (H_2 gas), (*S*)-isomer 59.1 min., (*R*)-isomer 66.2 min.).

(*R*)-1,1,1-Trichloropentan-2-ol (*R*)-40.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichloropentan-2-one **50** (191 mg, 1 mmol), [Ru(benzene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (141 mg, 73 %, 83 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 20.8 min., (*R*)-isomer 22.9 min.).

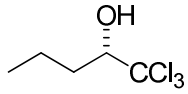
The title compound was synthesised using General Procedure 4 with 1,1,1-trichloropentan-2-one **50** (191 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (135 mg, 70 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 20.0 min., (*R*)-isomer 22.3 min.).

The title compound was synthesised using General Procedure 5 with 1,1,1-trichloropentan-2-one **50** (191 mg, 1 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) to give a colourless oil (137 mg, 71 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 39.9 min., (*R*)-isomer 42.8 min.).

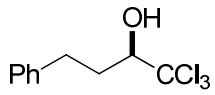
(*S*)-1,1,1-Trichloropentan-2-ol (*S*)-40.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichloropentan-2-one **50** (191 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (128 mg, 66 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 20.6 min., (*R*)-isomer 22.9 min.).

(*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*R*)-25.



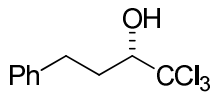
The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-4-phenylbutan-2-one **54** (252 mg, 1 mmol), [Ru(benzene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless solid (214 mg, 84 %, 89 % e.e.).

Spectroscopic data similar to that of racemate; m.p. 55-57 ºC; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 210 nm, (*S*)-isomer 10.35 min., (*R*)-isomer 17.33 min.).

The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-4-phenylbutan-2-one **54** (252 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless solid (246 mg, 97 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; m.p. 55-57 ºC; $[\alpha]_D^{23}$ (*c* 1.06, $CHCl_3$): + 44.2 (*R*) lit.[23]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 210 nm, (*S*)-isomer 10.36 min., (*R*)-isomer 17.52 min.).

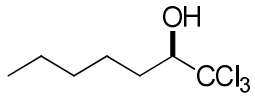
(*S*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*S*)-25.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-4-phenylbutan-2-one **54** (252 mg, 1 mmol), [Ru(benzene)Cl_2]$_2$ and (*S*,*S*)-TsDPEN to give a colourless oil (216 mg, 85 %, 88 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{23}$ (*c* 0.96, $CHCl_3$): - 41.3 (*S*) lit.[23]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 210 nm, (*S*)-isomer 10.37 min., (*R*)-isomer 17.71 min.).

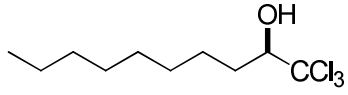
(*R*)-1,1,1-Trichloropropan-2-ol (*R*)-24.



The title compound was synthesised using 1,1,1-trichloroheptan-2-one **51** (218 g, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (185 mg, 84 %, 96 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{24}$ (*c* 0.28, $CHCl_3$): + 16.3 (*R*) lit.[24]; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas), (*S*)-isomer 36.9 min., (*R*)-isomer 38.2 min.).

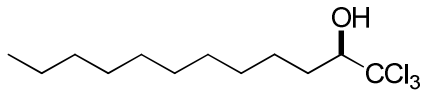
(*R*)-1,1,1-Trichlorodecan2-ol (*R*)-41.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichlorodecan-2-one **52** (261 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (237 mg, 90 %, 96 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 1.00, $CHCl_3$): + 20.9; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50 m 0.25 mm 0.25 μm, T = 150 °C, P = 15 psi (H_2 gas), (*S*)-isomer 58.5 min., (*R*)-isomer 59.8 min.).

(*R*)-1,1,1-Trichlorodecan-2-ol (*R*)-42.



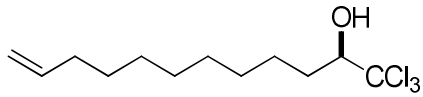
The title compound was synthesised using General Procedure 4 with 1,1,1-trichlorodecan-2-one **53** (288 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (244 mg, 84 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{27}$ (*c* 1.08, $CHCl_3$): + 20.5; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 160 °C, P = 15 psi (H_2 gas), (*S*)-isomer 71.7 min., (*R*)-isomer 74.3 min.).

The title compound was synthesised using General Procedure 5 with 1,1,1-trichlorodecan-2-one **53** (288 mg, 1 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) to give a colourless oil (206 mg, 71 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 160 °C, P = 15 psi (H_2 gas), (*S*)-isomer 72.6 min., (*R*)-isomer 75.7 min.).

(*R*)-1,1,1-Trichlorodec-9-en-2-ol (*R*)-43.



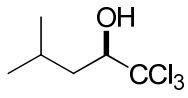
The title compound was synthesised using General Procedure 4 with 1,1,1-trichlorodec-9-en-2-one **63** (286 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (240 mg, 83 %, 94 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{26}$ (*c* 1.00, $CHCl_3$): + 19.2; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 160 °C, P = 15 psi (H_2 gas), (*S*)-isomer 74.7 min., (*R*)-isomer 77.3 min.).

The title compound was synthesised using General Procedure 5 with 1,1,1-trichlorodec-9-en-2-one **63** (286 mg, 1 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) to give a colourless oil (285 mg, 99 %, 96 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 160 °C, P = 15 psi (H_2 gas), (*S*)-isomer 74.7 min., (*R*)-isomer 77.3 min.).

(*R*)-1,1,1-Trichloro-4-methylpentan-2-ol (*R*)-44.

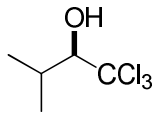


The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-4-methylpentan-2-one **55** (203 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (113 mg, 55 %, 97 % e.e.).

Spectroscopic data similar to that of racemate. $[\alpha]_D^{28}$ (*c* 1.80, $CHCl_3$): + 13.0; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m

0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas), (*S*)-isomer 16.5 min., (*R*)-isomer 17.9 min.).

(*R*)-1,1,1-Trichloro-3-methylbutan-2-ol (*R*)-46.



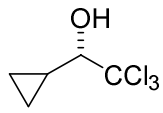
The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-3-methylbutan-2-one **58** (380 mg, 2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*R*,*R*)-TsDPEN to give a colourless oil (191 mg, 50 %, 83 % e.e.).

Spectroscopic data similar to that of racemate. $[\alpha]_D^{27}$ (*c* 0.76, $CHCl_3$): + 11.1; enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50 m 0.25 mm 0.25 μm, T = 110 °C, P = 15 psi (H_2 gas), (*S*)-isomer 19.7 min., (*R*)-isomer 20.6 min.).

The title compound was synthesised using General Procedure 5 with 1,1,1-trichloro-3-methylbutan-2-one **58** (190 mg, 1 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) to give a colourless oil (113 mg, 59 %, 99 % e.e.).

Spectroscopic data similar to that of racemate. Enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50 m 0.25 mm 0.25 μm, T = 110 °C, P = 15 psi (H_2 gas), (*S*)-isomer 31.2 min., (*R*)-isomer 31.7 min.).

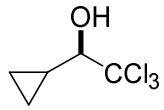
(*S*)-2,2,2-Trichloro-1-cyclopropylethanol 47.



The title compound was synthesised using 1,1,1-trichlorocyclopropylethan-2-one **59** (188 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*S*,*S*)-TsDPEN to give a colourless oil (112 mg, 59 %, 16 % e.e.).

Spectroscopic data similar to that of racemate. Enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 29.3 min., (*R*)-isomer 30.3 min.).

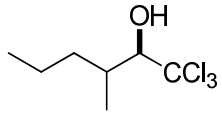
(*S*)-2,2,2-Trichloro-1-cyclopropylethanol 47.



The title compound was synthesised using 1,1,1-trichlorocyclopropylethan-2-one **59** (188 mg, 1 mmol) and (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) to give a colourless oil (126 mg, 66 %, 51 % e.e.).

Spectroscopic data similar to that of racemate. Enantiomeric excess determined by GC analysis on acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 43.3 min., (*R*)-isomer 44.5 min.).

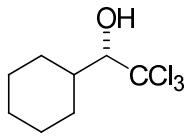
(2*R*)-1,1,1-Trichloro-3-methylpentan-2-ol (2*R*)-48.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichloro-3-methylpentan-2-one **60** (218 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (1'*R*,2'*R*)-TsDPEN to give a colourless oil (152 mg, 69 %, 91 and 89 % e.e., 57 : 43 d.r.).

Spectroscopic data similar to that of racemate. Enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50 m 0.25 mm 0.25 μm, T = 120 °C, P = 15 psi (H_2 gas), (2*S*)-diastereomer 1 40.6 min., (2*R*)-diastereomer 2 50.7, (2*R*)-diastereomer 1 49.1 min, (2*S*)-diastereomer 2 53.5 min. (2*S*)-diastereomer 1 40.6 min., (2*R*)-diastereomer 2 50.7, (2*R*)-diastereomer 1 49.1 min, (2*S*)-diastereomer 2 53.5 min.

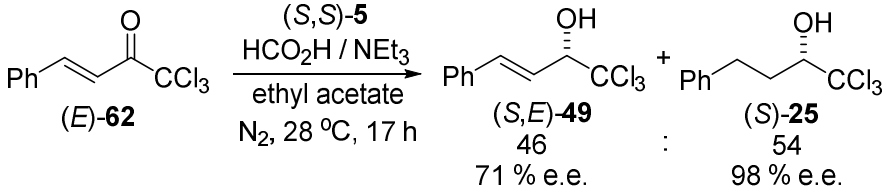
(*S*)-2,2,2-Trichloro-1-cyclohexylethanol (*R*)-26.



The title compound was synthesised using General Procedure 4 with 1,1,1-trichlorocyclohexylethan-2-one **61** (230 mg, 1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ and (*S*,*S*)-TsDPEN to give a colourless oil (202 mg, 88 %, 90 % e.e.).

Spectroscopic data similar to that of racemate. Enantiomeric excess determined by GC analysis (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas), (*S*)-isomer 35.4 min., (*R*)-isomer 37.9 min.).

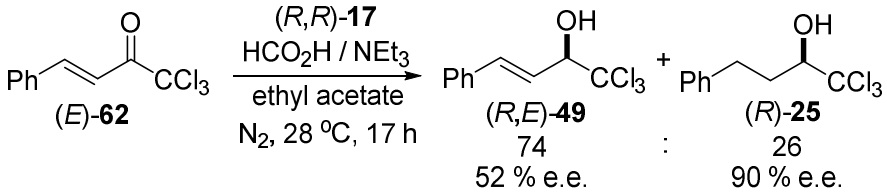
ATH of (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one (*E*)-62 with (*S*,*S*)-5.



The title compounds were synthesised using General Procedure 4 with (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one (*E*)-**62** (250 mg, 1 mmol), [Ru([-cymene)Cl_2]$_2$, (*S*,*S*)-TsDPEN and ethyl acetate (0.5 mL) to give a yellow oil consisting of a 46 : 54 mixture (by ^{1}H NMR spectroscopy) of (*S*,*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol (*S*,*E*)-**49** (71 % e.e.) and (*S*)-1,1,1-trichloro-4-phenylbutan-2-ol (*S*)-**25** (98 % e.e.) respectively.

Enantiomeric excesses determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*S*)-**25** 10.40 min., (*R*)-**25** 18.41 min., (*S*,*E*)-**49** 25.10 min., (*R*,*E*)-**49** 27.00 min.).

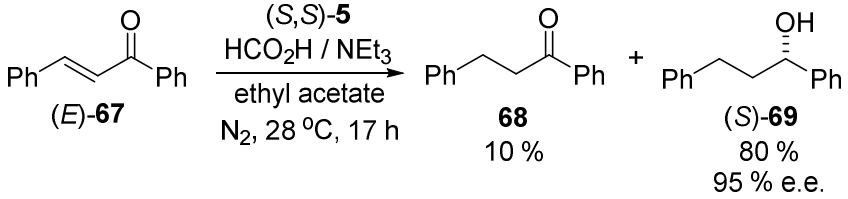
ATH of (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one (*E*)-62 with (*R*,*R*)-17.



The title compounds were synthesised using General Procedure 5 with (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one (*E*)-**62** (250 mg, 1 mmol), (*R*,*R*)-TsDPEN-teth-Ru-Cl (*R*,*R*)-**17** (3.1 mg) and ethyl acetate (0.5 mL) to give a yellow oil consisting of a 74 : 26 mixture (by ^{1}H NMR spectroscopy) of (*S*,*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol (*S*,*E*)-**49** (52 % e.e.) and (*S*)-1,1,1-trichloro-4-phenylbutan-2-ol (*S*)-**25** (90 % e.e.) respectively.

Enantiomeric excesses determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*S*)-**25** 10.01 min., (*R*)-**25** 16.23 min., (*S*,*E*)-**49** 23.46 min., (*R*,*E*)-**49** 25.09 min.).

ATH of *trans*-chalcone (*E*)-67 with (*S*,*S*)-5.



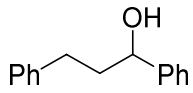
The title compounds were synthesised using General Procedure 4 with *trans*-chalcone (*E*)-**67** (208 mg, 1 mmol), [Ru([-cymene)Cl_2]$_2$, (*S*,*S*)-TsDPEN and ethyl acetate (0.5 mL). The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether) to give 1,3-diphenylpropan-1-one **68** as yellow oil (22 mg, 10 %) and (*S*)-1,3-diphenylpropan-1-ol (*S*)-**69** (168 mg, 80 %, 95 % e.e.).

Spectroscopic data are consistent with those from the independent synthesis of **68** and **69** (see **5.2.8**). Enantiomeric excess determined by HPLC analysis (Daicel Chiralcel

OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 209 nm, (*S*)-**69** 19.89 min., (*R*)-**68** 23.69 min.). Chromatographic data are consistent with that previously reported.[25]

5.2.8 Independent Synthesis of 1,3-Diphenylpropan-1-one 68 and 1,3-Diphenylpropan-1-ol 69.

1,3-Diphenylpropan-1-ol 69.

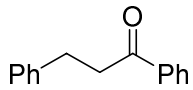


Method modified from the literature.[26]

To a solution phenyl lithium (1.8 M in dibutyl ether, 14 mL, 14 mmol, 1.4 equiv.) at -78 ºC under nitrogen was added dropwise a solution of hydrocinnamaldehyde (1.34 g, 10 mmol, 1 equiv.) in diethyl ether (14 mL). The resulting solution was allowed to warm to room temperature over 1 hour before being quenched by the dropwise addition of sat. aq. ammonium chloride (20 mL). The resulting mixture was extracted with diethyl ether (2 x 20 mL). Combined organics were washed with distilled water (20 mL) and sat. aq. sodium chloride (20 mL). The organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a light orange oil. The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a yellow oil (0.94 g, 44 %).

δ_H (300 MHz; $CDCl_3$) 7.34-7.05 (10H, m, Ar*H*), 4.59 (1H, dd, *J* 7.5 and 5.5, C*H*OH), 2.74-2.50 (2H, m, CH_2Ph), 2.12-1.87 (2H, m, CH_2CH), 1.84 (1H, br. s, O*H*). These data are consistent with that previously reported.[26]

1,3-Diphenylpropan-1-one 68.



Oxalyl chloride (0.44 mL, 5 mmol, 5 equiv.) was added dropwise to a solution of CH_2Cl_2 (9 mL) and DMSO (0.71 mL, 10 mmol, 10 equiv.) at -78 ºC under nitrogen. A solution of 1,3-diphenylpropan-1-ol **69** (212 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added dropwise at -78 ºC and the reaction was held at -78 ºC for 30 minutes before the dropwise addition of triethylamine (1.4 mL, 10 mmol, 10 equiv.). The resulting solution was stirred at -78 ºC for 15 minutes and then at room temperature for 1 hour. The reaction mixture was quenched with pH 2 buffer (15 mL) and then extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography (20 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (149 mg, 71 %).

δ_H (400 MHz; $CDCl_3$) 7.98-7.96 (2H, m, Ar*H*), 7.56 (1H, t, *J* 7, Ar*H*), 7.46 (2H, t, *J* 8, Ar*H*), 7.33-7.18 (5H, m, Ar*H*), 3.31 (2H, t, *J* 7.5, CH_2), 3.08 (2H, t, *J* 8, CH_2); δ_C (100 MHz; $CDCl_3$) 199.4 (*C*O), 141.3 (Ar$C_{quat.}$), 136.8 (Ar$C_{quat.}$), 133.0 (Ar*C*), 128.6 (Ar*C*), 125.5 (Ar*C*), 128.4 (Ar*C*), 128.0 (Ar*C*), 126.1 (Ar*C*), 40.4 (*C*H_2), 30.1 (*C*H_2). These data are consistent with that previously reported.[27, 28]

5.2.9 X-ray Crystallographic Data for (*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*R*)-25. Performed by Dr Guy J. Clarkson.

Single crystals of (*R*)-**25** were grown from the slow evaporation of ethyl acetate. A suitable crystal was selected and mounted on a mitogen loop with Fromblin oil on an Oxford Diffraction Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,[29] the structure was solved with the Superflip[30-32] structure solution program using Charge Flipping and

refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal Data for (*R*)-**25**: orthorhombic, space group $P22_12_1$ (no. 18), a = 5.88763(14) Å, b = 17.3853(3) Å, c = 11.03525(20) Å, V = 1129.55(4) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 7.058 mm^{-1}, *Dcalc* = 1.491 g/mm^3, 4029 reflections measured ($9.492 \leq 2\Theta \leq 155.074$), 2326 unique ($R_{int}$ = 0.0195, R_{sigma} = 0.0186) which were used in all calculations. The final R_1 was 0.0500 ($I > 2\sigma(I)$) and wR_2 was 0.1281 (all data).

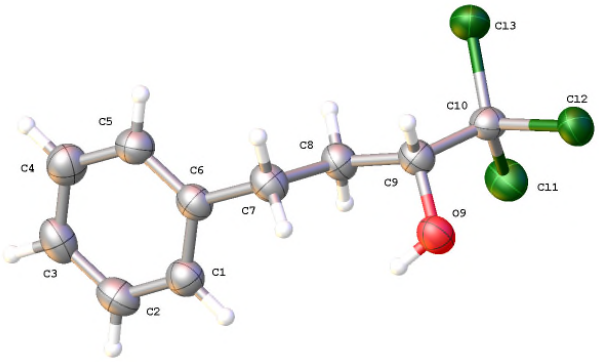


Figure 51 Solid state structure of (*R*)-**25** with atom labels. Thermal ellipsoids are drawn at 50% probability.

The asymmetric unit contains (*R*)-**25**. There are 4 molecules in the unit cell. The Flack parameter is 0.046(15) (Shelx 2013/14).[34] The Hooft y parameter refined to 0.036(6) (Olex2).[29]

5.3 EXPERIMENTAL FOR CHAPTER 2

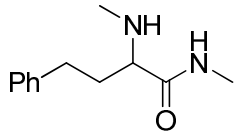
5.3.1 Synthesis of Amino-amides. General Procedure 6:

Trichloromethyl alcohol (1 mmol, 1 equiv.) and benzyltriethylammonium chloride (4.6 mg, 0.02 mmol, 0.02 equiv.) were stirred in CH_2Cl_2 (1 mL) on ice. Amine was added, and the mixture was stirred for 10 minutes before the dropwise addition of 40 % aq. NaOH (5 mmol). The reaction mixture was stirred for a further 15 minutes on ice before being allowed to warm to room temperature where it was stirred for 17 hours. Distilled water (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 15

mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography.

5.3.1.1 Racemic Products.

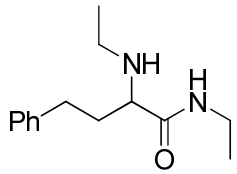
***N*-Methyl-2-(methylamino)-4-phenylbutanamide 142.**



N-Methyl-2-(methylamino)-4-phenylbutanamide **142** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), methylamine hydrochloride (675 mg, 10 mmol) and 40 % NaOH (3 mL, 30 mmol). The residue was purified by silica column chromatography (ethyl acetate to 30 % methanol in ethyl acetate) to give a yellow oil (126 mg, 61 %).

ν_{max}/cm^{-1} (neat) 3294 (br., NH st.), 2940 (m, CH st.), 1647 (s, C=O st.), 1532 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.30-7.26 (2H, m, Ar*H*), 7.20-7.18 (4H, m, Ar*H* and CON*H*), 3.02 (1H, dd, *J* 7 and 5.5, C*H*NH), 2.93 (1H, br. s, CHN*H*), 2.83 (3H, d, *J* 5, CONHC*H*$_3$), 2.69 (2H, m, C*H*$_2$Ph), 2.35 (3H, s, CHNHC*H*$_3$), 2.11-2.02 (1H, m, C*H*$_2$CHCO), 1.87 (1H, ddt, *J* 14, 9 and 7, C*H*$_2$CHCO); δ_C (100 MHz; $CDCl_3$) 173.9 (*C*O), 141.1 (Ar$C_{quat.}$), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.1 (Ar*C*), 64.4 (*C*H), 34.9 (CONH*C*H$_3$), 34.7 (*C*H$_2$CHCO), 32.2 (*C*H$_2$Ph), 25.8 (CHNH*C*H$_3$); HRMS (ESI) calc. for $C_{12}H_{19}N_2O$ (M + H$^+$) requires 207.1492, found 207.1490.

***N*-Ethyl-2-(ethylamino)-4-phenylbutanamide 143.**

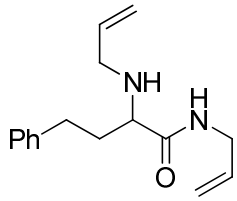


N-Ethyl-2-(ethylamino)-4-phenylbutanamide **143** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol) and 70 %

ethylamine in water (0.47 mL, 9 mmol). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a yellow oil (151 mg, 65 %).

ν_{max}/cm^{-1} (neat) 3309 (br., NH st.), 2969 (m, CH st.), 1644 (s, C=O st.), 1524 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.35-7.32 (2H, m, Ar*H*), 7.29-7.23 (4H, m, Ar*H* and CON*H*), 3.36 (2H, m, CONHC*H*$_2$), 3.13 (1H, dd, *J* 7.5 and 5, C*H*NH), 2.77 (2H, m, C*H*$_2$Ph), 2.61 (2H, q, *J* 7, CHNHC*H*$_2$), 2.13 (1H, dddd, *J* 14, 9, 7 and 5, C*H*$_2$CHCO), 1.90 (1H, ddt, *J* 14, 9 and 7, C*H*$_2$CHCO), 1.20 (3H, t, *J* 7, CONHCH$_2$C*H*$_3$), 1.11 (3H, t, *J* 7, CHNHCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 173.9 (*C*O), 141.2 (Ar$C_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*), 62.8 (*C*H), 43.0 (CONH*C*H$_2$), 35.3 (*C*H$_2$CHCO), 33.7 (CHNH*C*H$_2$), 32.4 (*C*H$_2$Ph), 15.3 (CONHCH$_2$*C*H$_3$), 14.9 (CHNHCH$_2$*C*H$_3$); HRMS (ESI) calc. for $C_{14}H_{23}N_2O$ (M + H$^+$) requires 235.1805, found 235.1811.

***N*-Allyl-2-(allylamino)-4-phenylbutanamide 144.**

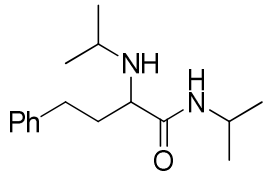


N-Allyl-2-(allylamino)-4-phenylbutanamide **144** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), allylamine (0.75 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (177 mg, 69 %).

ν_{max}/cm^{-1} (neat) 3306 (br., NH st.), 3082 (w, =CH$_2$ st.), 2923 (m, CH st.), 1641 (s, C=O st.), 1518 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.30-7.26 (3H, m, Ar*H*), 7.20-7.17 (3H, m, Ar*H* and CON*H*), 5.90-5.77 (2H, m, 2 x C*H*=CH$_2$), 5.20-5.07 (4H, m, 2 x CH=C*H*$_2$), 3.90 (2H, tt, *J* 6 and 1.5, CONHC*H*$_2$), 3.22-3.10 (3H, m, C*H*NH and CHNHC*H*$_2$), 2.72

(2H, t, *J* 8, C*H*$_2$Ph), 2.14-2.05 (1H, m, C*H*$_2$CHCO), 1.93-1.84 (1H, m, C*H*$_2$CHCO); δ_C (100 MHz; $CDCl_3$) 173.9 (*C*O), 141.1 (Ar$C_{quat.}$), 135.8 (*C*H=CH_2), 134.3 (*C*H=CH_2), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.1 (Ar*C*), 116.4 (CH=*C*H_2), 115.9 (CH=*C*H_2), 62.0 (*C*HNH), 51.1 (CHNH*C*H_2), 41.2 (CONH*C*H_2), 35.3 (*C*H_2CHCO), 32.4 (*C*H_2Ph); HRMS (ESI) calc. for $C_{16}H_{23}N_2O$ ($M + H^+$) requires 259.1805, found 259.1800.

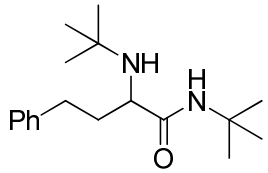
***N*-Isopropyl-2-(isopropylamino)-4-phenylbutanamide 145.**



N-Isopropyl-2-(isopropylamino)-4-phenylbutanamide **145** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), propan-2-amine (0.82 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (ethyl acetate) to give a yellow oil (178 mg, 68 %).

ν_{max}/cm^{-1} (neat) 3299 (br., NH st.), 2966 (m, CH st.), 1641 (s, C=O st.), 1520 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.35-7.32 (2H, m, Ar*H*), 7.29-7.22 (4H, m, Ar*H* and CON*H*), 4.12 (1H, m, CONHC*H*), 3.15 (1H, dd, *J* 8.0 and 4.5, C*H*NH), 2.81-2.70 (3H, m, C*H*$_2$Ph and CHNHC*H*Me_2), 2.18-2.10 (1H, m, C*H*$_2$CHCO), 1.86 (1H, ddt, *J* 15, 8 and 7, C*H*$_2$CHCO), 1.46 (1H, br. s, CHN*H*), 1.21 (3H, d, *J* 6.5, CONHCH(C*H*$_3$)$_2$), 1.20 (3H, d, *J* 6.5, CONHCH(C*H*$_3$)$_2$), 1.06 (3H, d, *J* 6.5, CHNHCH(C*H*$_3$)$_2$), 1.05 (3H, d, *J* 6.5, CHNHCH(C*H*$_3$)$_2$); δ_C (100 MHz; $CDCl_3$) 173.9 (*C*O), 141.3 (Ar$C_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*), 60.9 (*C*H), 48.7 (CONH*C*HMe_2), 40.6 (CHNH*C*HMe_2), 35.8 (*C*H_2CHCO), 32.5 (*C*H_2Ph), 23.4 (*C*H_3), 22.9 (2 x *C*H_3), 22.7 (*C*H_3); HRMS (ESI) calc. for $C_{16}H_{27}N_2O$ ($M + H^+$) requires 263.2123, found 263.2112.

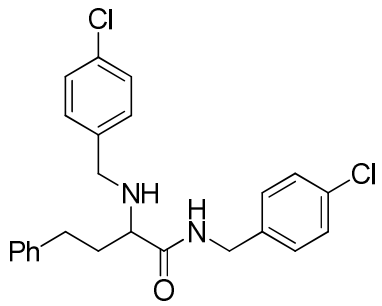
***N*-(*tert*-Butyl)-2-(*tert*-butylamino)-4-phenylbutanamide 146.**



N-(*tert*-Butyl)-2-(*tert*-butylamino)-4-phenylbutanamide **146** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), 2-methylpropan-2-amine (1.05 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a white solid (182 mg, 63 %).

m.p. 96-99 ºC; ν_{max}/cm^{-1} (neat) 3316 (br., NH st.), 2965 (m, CH st.), 1658 (s, C=O st.), 1522 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.58 (1H, br. s, CON*H*), 7.35-7.31 (2H, m, Ar*H*), 7.26-7.22 (3H, m, Ar*H*), 3.18 (1H, dd, *J* 7.5 and 4.5, C*H*NH), 2.72 (2H, m, CH_2Ph), 2.08 (1H, dddd, *J* 14.5, 10.5, 6.0 and 4.5, CH_2CHCO), 1.89-1.80 (1H, m, CH_2CHCO), 1.40 (9H, s, CONHC(CH_3)$_3$), 1.11 (9H, s, CHNHC(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 175.0 (*C*O), 141.4 (Ar$C_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*), 57.3 (*C*H), 51.3 (CONH*C*Me$_3$), 50.0 (CHNH*C*Me$_3$), 36.7 (*C*H$_2$CHCO), 32.4 (*C*H$_2$Ph), 29.3 (CONHC(*C*H$_3$)$_3$, 28.6 (CHNHC(*C*H$_3$)$_3$); HRMS (ESI) calc. for $C_{18}H_{31}N_2O$ (M + H$^+$) requires 291.2431, found 291.2434.

***N*-(4-Chlorobenzyl)-2-(4-chlorobenzyl)amino)-4-phenylbutanamide 147.**

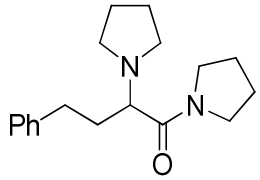


N-(4-Chlorobenzyl)-2-(4-chlorobenzyl)amino)-4-phenylbutanamide **147** was synthesised using General Procedure 1 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254

mg, 1 mmol), 4-chlorobenzylamine (0.61 mL, 5 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (20 % ethyl acetate in 40-60 petroleum ether to 50 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (315 mg, 74 %).

ν_{max}/cm^{-1} (neat) 3307 (br., NH st.), 1649 (s, C=O st.), 1490 (s, NH bend), 1089 (s, *p*-C-Cl skeletal vibrations); δ_H (400 MHz; $CDCl_3$) 7.49 (1H, br. t, *J* 6, CON*H*), 7.38-7.30 (6H, m, Ar*H*), 7.28-7.20 (5H, m, Ar*H*), 7.16-7.14 (2H, m, Ar*H*), 4.46 (2H, d, *J* 6, CONHC*H*$_2$), 3.70 (1H, d, *J* 13.5, CHNHC*H*H), 3.65 (1H, d, *J* 13.5, CHNHCH*H*), 3.25 (1H, dd, *J* 7.5 and 5, C*H*NH), 2.77 (2H, t, *J* 8, C*H*$_2$Ph), 2.21 (1H, dddd, *J* 15.5, 8.5, 7 and 5, C*H*$_2$CHCO), 2.01-1.92 (1H, m, C*H*$_2$CHCO), 1.74 (1H, br. s, CHN*H*); δ_C (100 MHz; $CDCl_3$) 173.8 (*C*O), 140.9 (Ar*C*$_{quat.}$), 137.7 (Ar*C*$_{quat.}$), 137.0 (Ar*C*$_{quat.}$), 133.2 (Ar*C*$_{quat.}$), 133.1 (Ar*C*$_{quat.}$), 129.4 (Ar*C*), 129.0 (Ar*C*), 128.8 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.2 (Ar*C*), 62.1 (*C*HNH), 52.0 (CHNH*C*H$_2$), 42.3 (CONH*C*H$_2$), 35.2 (*C*H$_2$CHCO), 32.3 (*C*H$_2$Ph); HRMS (ESI) calc. for $C_{24}H_{25}Cl^{35}{}_2N_2O$ (M + H^+) requires 427.1338, found 427.1346.

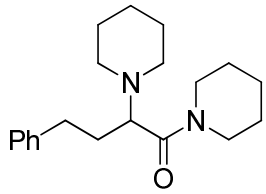
4-Phenyl-1,2-di(pyrrolidin-1-yl)butan-1-one 151.



4-Phenyl-1,2-di(pyrrolidin-1-yl)butan-1-one **151** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), pyrrolidine (0.82 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a colourless oil (261 mg, 91 %).

ν_{max}/cm^{-1} (neat) 2959 (m, CH st.), 1631 (s, C=O st.), 1431 (s, CH_2 bend); δ_H (400 MHz; $CDCl_3$) 7.35-7.31 (2H, m, Ar*H*), 7.26-7.22 (3H, m, Ar*H*), 3.63-3.50 (3H, m, 2 x CONC*H*H and CONCH*H*), 3.41 (1H, dd, *J* 9 and 5, C*H*N), 3.35 (1H, dt, *J* 6.5 and 3.5, CONCH*H*), 2.85-2.74 (3H, m, CHNC*H*$_2$ and C*H*$_2$Ph), 2.70-2.60 (3H, m, CHNC*H*$_2$ and C*H*$_2$Ph), 2.28 (1H, dtd, *J* 13.5, 9.5 and 5.5, C*H*$_2$CHCO), 2.08 (1H, dddd, *J* 16.5, 10, 6.5 and 5, C*H*$_2$CHCO), 2.00-1.85 (4H, m, CONCH$_2$C*H*$_2$), 1.84-1.76 (4H, m, CHNCH$_2$C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 170.6 (*C*O), 141.7 (Ar$C_{quat.}$), 128.2 (Ar*C*), 128.2 (Ar*C*), 125.7 (Ar*C*), 63.4 (*C*HN), 50.0 (CHN(*C*H$_2$)(*C*H$_2$)), 46.4 (CON(*C*H$_2$)CH$_2$), 45.5 (CON(CH$_2$)*C*H$_2$), 32.2 (*C*H$_2$Ph), 31.2 (*C*H$_2$CHCO), 26.1 (CHN(CH$_2$*C*H$_2$) (CH$_2$*C*H$_2$)), 24.0 (CON(CH$_2$*C*H$_2$) (CH$_2$*C*H$_2$)), 23.2 (CON(CH$_2$*C*H$_2$) (CH$_2$*C*H$_2$)); HRMS (ESI) calc. for $C_{18}H_{27}N_2O$ (M + H$^+$) requires 287.2118, found 287.2116.

4-Phenyl-1,2-di(piperidin-1-yl)butan-1-one 152.

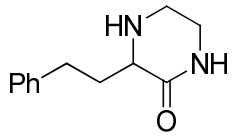


4-Phenyl-1,2-di(piperidin-1-yl)butan-1-one **152** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), piperidine (0.99 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (ethyl acetate) to give a colourless oil (209 mg, 67 %).

ν_{max}/cm^{-1} (neat) 2930 (m, CH st.), 1635 (s, C=O st.), 1440 (s, CH_2 bend); δ_H (400 MHz; $CDCl_3$) 7.28-7.24 (2H, m, Ar*H*), 7.20-7.15 (3H, m, Ar*H*), 3.83 (1H, ddd, *J* 13, 5.5 and 3.5, CON(C*H*H)CH$_2$), 3.55 (1H, ddd, *J* 13, 6 and 2.5, CON(CH$_2$)C*H*H), 3.37-3.26 (3H, m, C*H*N, CON(CH*H*)CH$_2$ and CON(CH$_2$)CH*H*), 2.70 (1H, ddd, *J* 14.5, 10 and 5, C*H*$_2$Ph), 2.55 (2H, dt, *J* 11 and 5.5, CHN(C*H*H)C*H*H), 2.44-2.36 (3H, m, C*H*$_2$Ph and CHN(CH*H*)CH*H*)), 2.18 (1H, dtd, *J* 13, 9.5 and 5, C*H*$_2$CHCO), 1.85 (1H, dddd, *J* 13.5,

10.5, 6.5 and 4, C*H*$_2$CHCO), 1.69-1.47 (10H, m, 5 x C*H*$_2$), 1.41-1.35 (2H, m, C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 169.7 (*C*O), 142.2 (Ar*C*$_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 125.7 (Ar*C*), 64.5 (*C*HN), 50.2 (CHN*C*H$_2$), 46.8 (CON*C*H$_2$), 43.0 (CON*C*H$_2$), 33.2 (*C*H$_2$Ph), 26.9 (*C*H$_2$), 26.7 (*C*H$_2$), 26.6 (*C*H$_2$), 26.1 (*C*H$_2$), 24.7 (*C*H$_2$), 24.5 (*C*H$_2$); HRMS (ESI) calc. for $C_{20}H_{31}N_2O$ ($M + H^+$) requires 315.2431, found 315.2433.

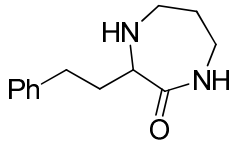
3-Phenethylpiperazin-2-one 140.



3-Phenethylpiperazin-2-one **140** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), 1,2-diaminoethane (0.67 mL, 10 mmol) and 40 % aq. NaOH (0.5 mL, 5 mmol) in CH_2Cl_2 (5 mL). The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % methanol in CH_2Cl_2) to give a yellow solid (187 mg, 92 %).

m.p. 146-147 ºC; ν_{max}/cm^{-1} (neat) 3222 (w, amine NH st.), 3025 (w, lactam NH st.), 1652 (s, C=O st.), 1492 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.32-7.19 (5H, m, Ar*H*), 6.47 (1H, br. s, CON*H*), 3.48-3.41 (2H, m, C*H* and CONHC*H*$_2$), 3.31 (1H, dq, *J* 11.5 and 4, CONHC*H*$_2$), 3.17 (1H, dt, *J* 13 and 4, HCNHC*H*$_2$), 2.99 (1H, ddd, *J* 13, 9.5 and 4, HCNHC*H*$_2$), 2.87-2.73 (2H, m, C*H*$_2$Ph), 2.33 (1H, dddd, *J* 14, 10.5, 7 and 4, C*H*HCHCO), 2.05-1.95 (1H, m, CH*H*CHCO), 1.93 (1H, br. s, CHN*H*); δ_C (100 MHz; $CDCl_3$) 172.3 (*C*O), 141.5 (Ar*C*$_{quat.}$), 128.5 (Ar*C*), 128.4 (Ar*C*), 125.9 (Ar*C*), 58.3 (*C*H), 43.2 (*C*H$_2$), 41.3 (*C*H$_2$), 33.6 (*C*H$_2$), 32.1 (*C*H$_2$); HRMS (ESI) calc. for $C_{14}H_{17}N_2O$ ($M+H^+$) 205.1335, found 205.1335.

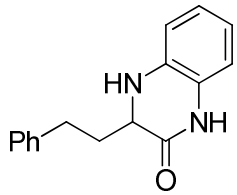
3-Phenethyl-1,4-diazepan-2-one 153.



3-Phenethyl-1,4-diazepan-2-one **153** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), 1,3-diaminopropane (0.83 mL, 10 mmol), 40 % aq. NaOH (0.6 mL, 6 mmol) in CH_2Cl_2 (10 mL). The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % methanol in CH_2Cl_2) to give a yellow solid (111 mg, 51 %).

m.p. 94-96 ºC; ν_{max}/cm^{-1} (neat) 3337 (w, amine NH st.), 3187 (w, lactam NH st.), 1654 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.34-7.30 (2H, m, Ar*H*), 7.26-7.19 (3H, m, Ar*H*), 6.50 (1H, br. s, N*H*CO), 3.40 (1H, dt, *J* 14 and 3.5, CH_2NHCH), 3.36-3.27 (2H, m, C*H*$_2$NHCO), 3.22 (1H, dd, *J* 8 and 5.5, C*H*), 2.89 (1H, ddd, *J* 14.5, 11.5 and 3.5, C*H*$_2$NH), 2.87-2.74 (2H, m, C*H*$_2$Ph), 2.21 (1H, dddd, *J* 14, 8.5, 7.5 and 5.5, C*H*$_2$CH$_2$Ph), 1.85 (1H, dtd, *J* 14, 8 and 6, C*H*$_2$CH$_2$Ph), 1.73 (1H, dtd, *J* 14, 5 and 3.5, *CH*$_2$CH$_2$N) 1.63 (1H, qt, *J* 14.5 and 3.5, C*H*$_2$CH$_2$N); δ_C (100 MHz; $CDCl_3$) 178.7 (*C*O), 142.0 (Ar*C*$_{quat.}$), 128.5, (Ar*C*), 128.3 (Ar*C*), 125.7 (Ar*C*), 59.0 (*C*H), 50.3 (*C*H$_2$NHCH), 41.4 (*C*H$_2$NHCO), 33.2 (*C*H$_2$CH$_2$Ph), 32.2 (*C*H$_2$Ph), 31.4 (*C*H$_2$CH$_2$N); HRMS (ESI) calc. for $C_{13}H_{18}N_2O$ ($M+H^+$) 219.1493, found 219.1492.

3-Phenethyl-3,4-dihydro-1*H*-quinoxalin-2-one 154.

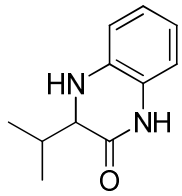


3-Phenethyl-3,4-dihydro-1*H*-quinoxalin-2-one **154** was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol), *o*-phenylenediamine (270 mg, 2.5 mmol) and 40 % aq. NaOH (0.5 mL, 5 mmol) in

CH_2Cl_2 (5 mL). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a yellow oil (132 mg, 52 %).

ν_{max}/cm^{-1} (neat) 3350 (w, amine NH st.), 3207 (w, lactam NH st.), 1667 (s, amide C=O st.), 1602 (m, amine NH bend); δ_H (400 MHz; $CDCl_3$) 8.91 (1H, br. s, N*H*CO), 7.35-7.31 (2H, m, Ar*H*), 7.26-7.23 (2H, m, Ar*H*), 6.94-6.88 (1H, m, Ar*H*), 6.81-6.76 (2H, m, Ar*H*), 6.59 (1H, d, *J* 7.5, Ar*H*), 3.99 (1H, dd, *J* 8 and 4.5, C*H*CO), 3.60 (1H, br. s, N*H*CH), 2.91-2.79 (2H, m, C*H*$_2$Ph), 2.25 (1H, dddd, *J* 13.5, 8.5, 7 and 4.5, C*H*$_2$CH), 2.09 (1H, br. dq, *J* 15.5 and 7.5, *CH*$_2$CH); δ_C (100 MHz; $CDCl_3$) 168.9 (*C*=O), 140.9 (Ar*C*$_{quat.}$), 132.8 (Ar*C*$_{quat.}$), 128.6 (Ar*C*), 128.4 (Ar*C*), 126.2 (Ar*C*), 125.3 (Ar*C*$_{quat.}$), 123.9 (Ar*C*), 119.5 (Ar*C*), 115.4 (Ar*C*), 114.2 (Ar*C*), 56.1 (*C*HCO), 33.3 (*C*H$_2$CH), 31.9 (*C*H$_2$Ph); HRMS (ESI) calc. for $C_{16}H_{17}N_2O$ (M+H$^+$) 253.1335, found 253.1336.

3-Isopropyl-3,4-dihydro-1H-quinoxalin-2-one 155.



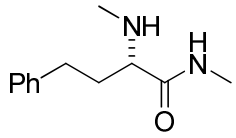
3-Isopropyl-3,4-dihydro-1*H*-quinoxalin-2-one **155** was synthesised using General Procedure 6 with 1,1,1-trichloro-3-methylbutan-2-ol **25** (192 mg, 1 mmol), *o*-phenylenediamine (270 mg, 2.5 mmol) and 40 % aq. NaOH (0.5 mL, 5 mmol) in CH_2Cl_2 (5 mL). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a light yellow solid (62 mg, 33 %).

m.p. 99-100 ºC; ν_{max}/cm^{-1} (neat) 3338 (w, NH amine st.), 3208 (w, lactam NH st.), 1665 (s, amide C=O st.), 1603 (m, amine NH bend); δ_H (400 MHz; $CDCl_3$) 9.52 (1H, br s, N*H*CO), 6.86 (1H, td, *J* 7.5 and 1.5, Ar*H*), 6.75 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 6.70 (1H, d, *J* 7.5, Ar*H*), 6.65 (1H, d, *J* 8, Ar*H*), 4.07 (1H, br. s, N*H*CH), 3.77 (1H, d, *J* 4.5, C*H*NH), 2.24 (1H, oct., *J* 5.5, C*H*(CH$_3$)$_2$), 1.04 (1H, d, *J* 7, C*H*$_3$), 0.97 (1H, d, *J* 7,

C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 168.6 (*C*O), 133.2 (Ar$C_{quat.}$), 124.8 (Ar$C_{quat.}$), 123.8 (Ar*C*), 118.7 (Ar*C*), 115.3 (Ar*C*), 113.3 (Ar*C*), 61.7 (*C*HNH), 30.8 (*C*H), 18.9 (*C*H$_3$), 17.4 (*C*H$_3$); HRMS (ESI) calc. for $C_{11}H_{15}N_2O$ ($M+H^+$) 191.1179, found 191.1184; calc. for $C_{11}H_{14}N_2NaO$ ($M+Na^+$) 213.0998, found 213.1002. These data are consistent with that previously reported.[35]

5.3.1.2 Enantiomerically enriched products.

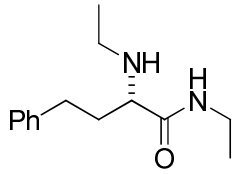
(*S*)-*N*-Methyl-2-(methylamino)-4-phenylbutanamide (*S*)-142.



(*S*)-*N*-Methyl-2-(ethylamino)-4-phenylbutanamide (*S*)-**142** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.), methanamine hydrochloride (675 mg, 10 mmol) and 40 % NaOH (3 mL, 30 mmol). The residue was purified by silica column chromatography (ethyl acetate to 20 % methanol in ethyl acetate) to give a yellow oil (134 mg, 65 %, 92 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{36}$ (*c* 0.14, $CHCl_3$): + 4.9 (*S*); enantiomeric excess determined by HPLC analysis on *N*-acyl derivative (*S*)-**148**.

(*S*)-*N*-Ethyl-2-(ethylamino)-4-phenylbutanamide (*S*)-143.

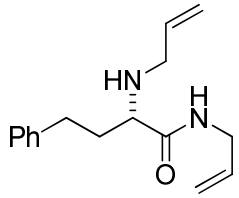


(*S*)-*N*-Ethyl-2-(ethylamino)-4-phenylbutanamide (*S*)-**143** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and 70 % ethylamine in water (0.46 mL, 9 mmol) and 40 % NaOH (0.5 mL, 5

mmol). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a yellow oil (162 mg, 69 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{\mathrm{D}}^{29}$ (c 0.25, $CHCl_3$): - 26.4 (*S*); enantiomeric excess determined by HPLC analysis on *N*-acyl derivative (*S*)-**149**.

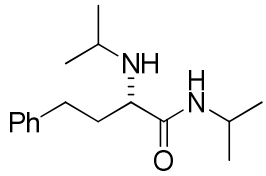
(*S*)-*N*-Allyl-2-(allylamino)-4-phenylbutanamide (*S*)-144.



(*S*)-*N*-Allyl-2-(allylamino)-4-phenylbutanamide (*S*)-**144** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), allylamine (0.75 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (181 mg, 70 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{\mathrm{D}}^{30}$ (c 1.15, $CHCl_3$): - 6.4 (*S*); enantiomeric excess determined by HPLC analysis on *N*-acyl derivative (*S*)-**150**.

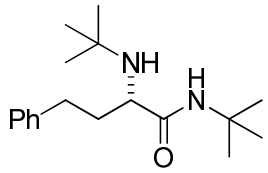
(*S*)-*N*-Isopropyl-2-(isopropylamino)-4-phenylbutanamide (*S*)-145.



(*S*)-*N*-Isopropyl-2-(isopropylamino)-4-phenylbutanamide (*S*)-**145** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), propan-2-amine (0.82 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (ethyl acetate) to give a yellow oil (182 mg, 69 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{30}$ (*c* 0.77, $CHCl_3$): - 35.0 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 0.5 mL/min., 208 nm, (*S*)-isomer 15.73 min., (*R*)-isomer 20.83 min.).

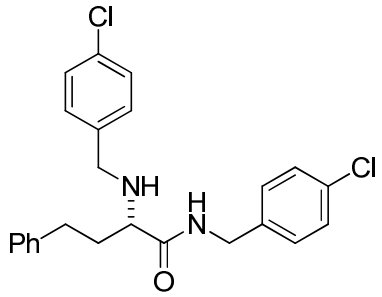
(*S*)-*N*-(*tert*-Butyl)-2-(tert-butylamino)-4-phenylbutanamide (*S*)-146.



(*S*)-*N*-(*tert*-Butyl)-2-(*tert*-butylamino)-4-phenylbutanamide (*S*)-**146** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 92 % e.e.), 2-methylpropan-2-amine (1.05 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-40 petroleum ether) to give a white solid (170 mg, 59 %, 95 % e.e.). A sample was taken and recrystallised from ethyl acetate/hexane for single crystal X-ray diffraction studies (see X-ray crystallographic data section).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 1.30, $CHCl_3$): - 25.2 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 208 nm, (*S*)-isomer 4.83 min., (*R*)-isomer 15.32 min.).

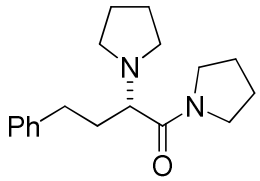
(*S*)-*N*-(4-Chlorobenzyl)-2-(4-chlorobenzyl)amino)-4-phenylbutanamide (*S*)-147.



(*S*)-*N*-(4-Chlorobenzyl)-2-(4-chlorobenzyl)amino)-4-phenylbutanamide (*S*)-**147** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.), 4-chlorobenzylamine (0.61 mL, 5 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (20 % ethyl acetate in 40-60 petroleum ether to 50 % ethyl acetate in 40-60 petroleum ether) to give a beige solid (281 mg, 66 %, 93 % e.e.). A sample was taken and recrystallised from benzene/hexane for single crystal X-ray diffraction studies (see X-ray crystallographic data section).

Spectroscopic data similar to that of racemate; m.p. 73-74 °C; $[\alpha]_{D}^{36}$ (*c* 0.63, $CHCl_3$): -7.5 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 217 nm, (*S*)-isomer 17.12 min., (*R*)-isomer 21.53 min.).

(*S*)-4-Phenyl-1,2-di(pyrrolidin-1-yl)butan-1-one (*S*)-151.

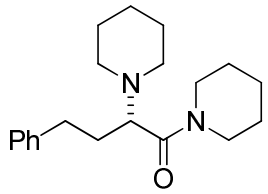


(*S*)-4-Phenyl-1,2-di(pyrrolidin-1-yl)butan-1-one (*S*)-**151** was synthesised using General Procedure 1 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), pyrrolidine (0.82 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue

was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a colourless oil (252 mg, 88 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{27}$ (*c* 0.56, $CHCl_3$): + 32.8 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*R*)-isomer 15.28 min., (*S*)-isomer 19.29 min.).

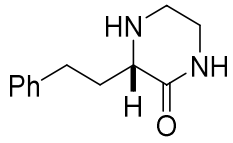
(*S*)-4-Phenyl-1,2-di(piperidin-1-yl)butan-1-one (*S*)-152.



(*S*)-4-Phenyl-1,2-di(piperidin-1-yl)butan-1-one (*S*)-**152** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), piperidine (0.99 mL, 10 mmol) and 40 % NaOH (0.5 mL, 5 mmol). The residue was purified by silica column chromatography (ethyl acetate) to give a colourless oil (228 mg, 73 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (*c* 1.32, $CHCl_3$): +12.3 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 0.5 mL/min., 208 nm, (*R*)-isomer 14.29 min., (*S*)-isomer 17.03 min.).

(*S*)-3-Phenethylpiperazin-2-one (*S*)-140.

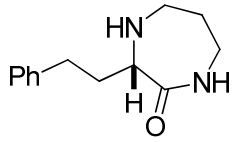


(*S*)-3-Phenethylpiperazin-2-one (*S*)-**140** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), 1,2-diaminoethane (0.67 mL, 10 mmol) and 40 % aq. NaOH (0.5 mL, 5 mmol) in CH_2Cl_2 (5

mL). The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % methanol in CH_2Cl_2) to give a yellow solid (187 mg, 92 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{25}$ (*c* 0.24, MeOH): - 30.8 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 50 : 50, 0.5 mL/min., 210 nm, (*S*)-isomer 11.97 min., (*R*)-isomer 14.64 min.).

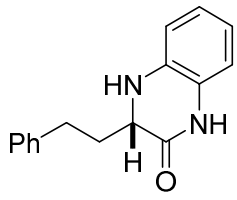
(*S*)-3-Phenethyl-1,4-diazepan-2-one (*S*)-153.



(*S*)-3-Phenethyl-1,4-diazepan-2-one (*S*)-**153** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), 1,3-diaminopropane (0.83 mL, 10 mmol), 40 % aq. NaOH (0.6 mL, 6 mmol) in CH_2Cl_2 (10 mL). The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % methanol in CH_2Cl_2) to give a yellow solid (111 mg, 51 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{23}$ (c 1.04, $CHCl_3$): - 31.6; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane : 2-propanol = 50 : 50, 0.5 mL/min., 212 nm, (*R*)-isomer 13.43 min., (*S*)-isomer 20.25 min.).

(*S*)-3-Phenethyl-3,4-dihydro-1*H*-quinoxalin-2-one (*S*)-154.

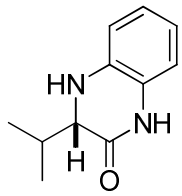


(*S*)-3-Phenethyl-3,4-dihydro-1*H*-quinoxalin-2-one (*S*)-**154** was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 97 % e.e.), *o*-phenylenediamine (270 mg, 2.5 mmol) and 40 % aq. NaOH (0.5

mL, 5 mmol) in CH_2Cl_2 (5 mL). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a yellow oil (132 mg, 52 %, 97 % e.e.).

Spectroscopic data similar to racemate; $[\alpha]_D^{23}$ (c 0.95, $CHCl_3$): + 10.1; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane : 2-propanol = 90 : 10, 1 mL/min., 222 nm, (*S*)-isomer 26.49 min., (*R*)-isomer 31.85 min.).

(*S*)-3-Isopropyl-3,4-dihydro-1H-quinoxalin-2-one (*S*)-155.



(*S*)-3-Isopropyl-3,4-dihydro-1*H*-quinoxalin-2-one (*S*)-**155** was synthesised using General Procedure 6 with 1,1,1-trichloro-3-methylbutan-2-ol (*R*)-**25** (192 mg, 1 mmol, 99 % e.e.), *o*-phenylenediamine (270 mg, 2.5 mmol) and 40 % aq. NaOH (0.5 mL, 5 mmol) in CH_2Cl_2 (5 mL). The residue was purified by silica column chromatography (ethyl acetate to 10 % methanol in ethyl acetate) to give a light yellow solid (120 mg, 63 %, 98 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{23}$ (c 0.56, $CHCl_3$): + 17.1 (*S*) lit.[35]; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane : 2-propanol = 90 : 10, 1 mL/min., 224 nm, (*S*)-isomer 12.51 min., (*R*)-isomer 17.48 min.).

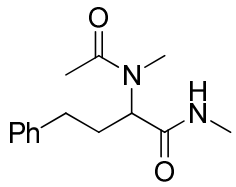
5.3.2 Synthesis of *N*-Acyl Derivatives. General Procedure 7:

Amino-amide (1 equiv.) and pyridine (2 equiv.) were stirred in CH_2Cl_2 on ice for 5 minutes before the dropwise addition of acetyl chloride (1.2 equiv.). The reaction mixture was stirred for a further 10 minutes on ice before being allowed to warm to

room temperature where it was stirred for 17 hours. Then pH 2 buffer was added and the reaction mixture was extracted twice with CH_2Cl_2. Organic layer was extracted with sat. aq. sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography.

5.3.2.1 Racemic Products.

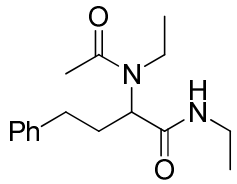
_N_-Methyl-2-(_N_-methylacetamido)-4-phenylbutanamide 148.



N-Methyl-2-(*N*-methylacetamido)-4-phenylbutanamide **148** was synthesised using General Procedure 7 with *N*-methyl-2-(methylamino)-4-phenylbutanamide **142** (196 mg, 0.95 mmol), CH_2Cl_2 (1.5 mL), acetyl chloride (100 μL, 1.4 mmol), pyridine (150 μL, 1.9 mmol). The residue was purified by silica column chromatography (ethyl acetate to 20 % methanol in ethyl acetate) to give a yellow oil (113 mg, 48 %).

ν_{max}/cm^{-1} (neat) 3308 (br., NH st.), 2936 (w, CH st.), 1627 (s, C=O st.), 1533 (m, NH bend), 1401 (s, CN stretch); δ_H (400 MHz; $CDCl_3$) 7.30-7.05 (5H, m, Ar*H*), 6.19 (1H, br. s, N*H*), 4.93 (1H, br. t, *J* 7.5, C*H*N), 2.83 (3H, s, CHNC*H*$_3$), 2.70 (3H, d, NHC*H*$_3$), 2.60-2.40 (2H, m, C*H*$_2$Ph), 2.25-2.14 (1H, m, C*H*HCHCO), 2.04 (3H, s, COC*H*$_3$), 1.96-1.83 (1H, m, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 171.9 (*C*OCH$_3$), 170.9 (*C*ONH), 141.0 (Ar*C*$_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.1 (Ar*C*), 55.6 (*C*H), 32.4 (*C*H$_2$Ph), 31.4 (CO*C*H$_3$), 29.3 (*C*H$_2$CHCO), 26.0 (CONH*C*H$_3$), 22.1 (CHN*C*H$_3$); HRMS (ESI) calc. for $C_{14}H_{20}N_2NaO_2$ (M + Na$^+$) requires 271.1417, found 271.1420.

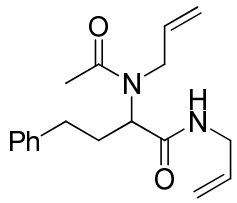
***N*-Ethyl-2-(*N*-ethylacetamido)-4-phenylbutanamide 149.**



N-Ethyl-2-(*N*-ethylacetamido)-4-phenylbutanamide **149** was synthesised using General Procedure 7 with *N*-Ethyl-2-(ethylamino)-4-phenylbutanamide **143** (23 mg, 0.1 mmol), CH_2Cl_2 (1 mL), acetyl chloride (8.5 μL, 0.12 mmol), pyridine (17 μL, 0.2 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a yellow oil (18 mg, 65 %).

ν_{max}/cm^{-1} (neat) 3299 (br., NH st.), 2930 (m, CH st.), 1677 (s, C=O st.), 1628 (s, CON st.), 1525 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.29-7.26 (2H, m, Ar*H*), 7.20-7.17 (3H, m, Ar*H*), 6.50 (1H, br. s, N*H*), 4.83 (1H, t, *J* 7.5, C*H*N), 3.38-3.32 (2H, m, CHNC*H*$_2$), 3.27-3.20 (2H, m, CONHC*H*$_2$), 2.63 (1H, ddd, *J* 13.5, 10 and 6, C*H*$_2$Ph), 2.56-2.50 (1H, m, C*H*$_2$Ph), 2.36-2.27 (1H, m, C*H*$_2$CHCO), 2.15 (3H, s, COC*H*$_3$), 2.02-1.93 (1H, m, C*H*$_2$CHCO), 1.16 (3H, t, *J* 7, NCH$_2$C*H*$_3$), 1.10 (3H, t, *J* 7, NHCH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 172.0 (*C*OCH$_3$), 171.0 (*C*ONH), 141.1 (Ar*C*$_{quat.}$), 128.40 (Ar*C*), 128.39 (Ar*C*), 126.0 (Ar*C*), 56.7 (*C*H), 40.4 (CON*C*H$_2$), 34.1 (CHNH*C*H$_2$), 32.5 (*C*H$_2$Ph), 30.0 (*C*H$_2$CHCO), 21.8 (CO*C*H$_3$), 15.1 (*C*H$_3$), 14.7 (*C*H$_3$); HRMS (ESI) calc. for $C_{16}H_{24}N_2NaO_2$ (M + Na$^+$) requires 299.1730, found 299.1732.

***N*-Allyl-2-(*N*-allylacetamido)-4-phenylbutanamide 150.**



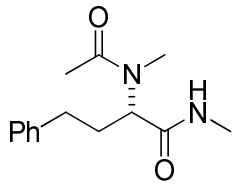
N-Allyl-2-(*N*-allylacetamido)-4-phenylbutanamide **150** was synthesised using General Procedure 7 with *N*-allyl-2-(allylamino)-4-phenylbutanamide **144** (52 mg, 0.2 mmol),

CH_2Cl_2 (2 mL), acetyl chloride (17 μL, 0.24 mmol) and pyridine (34 μL, 0.4 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (35 mg, 58 %).

ν_{max}/cm^{-1} (neat) 3314 (br., NH st.), 2974 (m, =CH st.), 2934 (m, CH st.), 1660 (s, CO st.), 1531 (m, NH bend), 1420 (m, =CH bend); δ_H (400 MHz; $CDCl_3$) 7.28-7.24 (2H, m, Ar*H*), 7.19-7.15 (3H, m, Ar*H*), 6.54 (1H, br. s, N*H*), 5.84-5.70 (2H, m, 2 x C*H*=CH_2), 5.18-5.08 (4H, m, CH=C*H*$_2$), 4.94 (1H, dd, *J* 8 and 7, C*H*N), 3.94-3.92 (2H, m, CHNC*H*$_2$), 3.84-3.81 (2H, m, CONHC*H*$_2$), 2.64 (1H, ddd, *J* 15.5, 10 and 6, C*H*HPh), 2.52 (1H, ddd, *J* 15.5, 9.5 and 6.5, CH*H*Ph), 2.34-2.45 (1H, m, C*H*HCHCO), 2.10 (1H, s, C*H*$_3$), 1.98-1.90 (1H, m, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 172.6 (*C*OCH_3), 170.4 (*C*ONH), 141.0 (Ar$C_{quat.}$), 133.9 (*C*H=CH_2), 133.8 (*C*H=CH_2), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.1 (Ar*C*), 117.1 (CH=*C*H_2), 116.2 (CH=*C*H_2), 56.6 (*C*H), 47.9 (CHNH*C*H_2), 41.6 (CONH*C*H_2), 32.5 (*C*H_2Ph), 29.9 (*C*H_2CHCO), 22.0 (*C*H_3); HRMS (ESI) calc. for $C_{18}H_{24}N_2NaO_2$ ($M + Na^+$) requires 323.1730, found 323.1734.

5.3.2.2 Enantiomerically enriched products.

(*S*)-*N*-Methyl-2-(*N*-methylacetamido)-4-phenylbutanamide (*S*)-148.

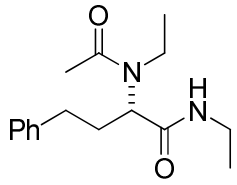


(*S*)-*N*-Methyl-2-(*N*-methylacetamido)-4-phenylbutanamide (*S*)-**148** was synthesised using General Procedure 7 with (*S*)-*N*-methyl-2-(methylamino)-4-phenylbutanamide (*S*)-**142** (0.103 mg, 0.5 mmol), CH_2Cl_2 (1 mL), acetyl chloride (53 μL, 0.75 mmol) and pyridine (80 μL, 1 mmol). The residue was purified by silica column chromatography

(ethyl acetate to 20 % methanol in ethyl acetate) to give a colourless oil (65 mg, 52 %, 92 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{36}$ (c 0.15, $CHCl_3$): + 76.0 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*R*)-isomer 20.33 min., (*S*)-isomer 27.37 min.).

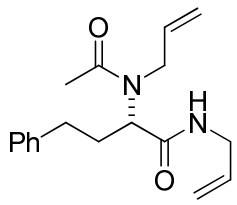
(*S*)-*N*-Ethyl-2-(*N*-ethylacetamido)-4-phenylbutanamide (*S*)-149.



(*S*)-*N*-Ethyl-2-(*N*-ethylacetamido)-4-phenylbutanamide (*S*)-**149** was synthesised using General Procedure 7 with (*S*)-*N*-ethyl-2-(ethylamino)-4-phenylbutanamide (*S*)-**143** (23 mg, 0.1 mmol), CH_2Cl_2 (1 mL), acetyl chloride (8.5 μL, 0.12 mmol) and pyridine (17 μL, 0.2 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (23 mg, 83 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.2, $CHCl_3$): - 60.5 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 208 nm, (*S*)-isomer 7.89 min., (*R*)-isomer 9.19 min.).

(*S*)-*N*-Allyl-2-(*N*-allylacetamido)-4-phenylbutanamide (*S*)-150.



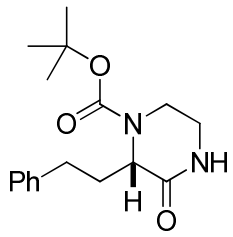
(*S*)-*N*-Allyl-2-(N-allylacetamido)-4-phenylbutanamide (*S*)-**150** was synthesised using General Procedure 7 with (*S*)-*N*-allyl-2-(allylamino)-4-phenylbutanamide (*S*)-**144** (52

mg, 0.2 mmol), acetyl chloride (17 μL, 0.24 mmol) and pyridine (34 μL, 0.4 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether) to afford a colourless oil (38 mg, 63 %, 97 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (*c* 0.28, $CHCl_3$): + 93.6 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*S*)-isomer 15.04 min., (*R*)-isomer 17.87 min.).

5.3.4 Synthesis of 1-Substituted Piperazin-2-ones *via N*-Amino Alkylation.

5.3.4.1 *N*-Boc-protection of (*S*)-3-Phenethylpiperazin-2-one (*S*)-140.

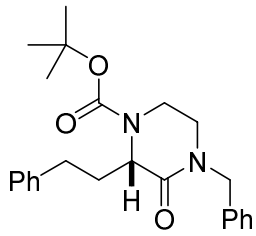


To a solution of (*S*)-3-phenethylpiperazin-2-one (*S*)-**140** (355 mg, 1.74 mmol, 96 % e.e.) in dry THF (16 mL) was added 40 % aq. NaOH (0.365 mL, 3.65 mmol, 2.1 equiv.). To this solution was added dropwise di-*tert*-butyl dicarbonate (456 mg, 2.1 mmol, 1.2 equiv.) in dry THF (1 mL). The reaction mixture was stirred at room temperature for 17 hours. THF was removed *in vacuo*, the residue taken up in ethyl acetate (20 mL) and washed with pH 2 buffer (2 x 20 mL). Organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford (*S*)-*tert*-butyl-3-oxo-2-phenethylpiperazine-1-carboxylate (*S*)-**156** as an orange solid (300 mg, 99 %, 94 % e.e.).

m.p. 138-140 ºC; ν_{max}/cm^{-1} (neat) 3189 (br., NH st.), 1695 (s, C=O st.), 1658 (s, C=O st.), 1333 (s, C-N st.), 1153 (s, C-O st.); δ_H (400 MHz; $CDCl_3$) 7.35-7.31 (2H, m, Ar*H*),

7.26-7.11 (3H, m, Ar*H*), 6.98 (1H, br. s, N*H*), 4.69 (1H, br. s, C*H*CO), 4.27 (1H, br. s, C*H*HNBoc), 3.52 (1H, td, *J* 11.5 and 3.5, C*H*HNH), 3.32-3.27 (1H, m, CH*H*NH), 3.25-3.19 (1H, m, CH*H*NBoc), 2.87-2.71 (2H, m, CH_2Ph), 2.35 (1H, dddd, *J* 14, 9.5, 6 and 4.5, C*H*HCHCO), 2.07 (1H, dddd, *J* 14, 11, 9.5 and 5, CH*H*CHCO), 1.51 (9H, s, 3 x CH_3); δ_C (100 MHz; $CDCl_3$) 171.0 (*C*O lactam), 154.1 (*C*O Boc), 151.3 (Ar$C_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*), 80.8 (*C*$(CH_3)_3$), 57.1 (C*H*N), 41.3 (*C*H_2NH), 36.4 (*C*H_2NBoc), 33.8 (*C*H_2CHCO), 32.5 (CH_2*C*H_2Ph), 28.3 (3 x *C*H_3); HRMS (ESI) calc. for $C_{17}H_{24}N_2NaO_3$ ($M+Na^+$) 327.1684, found 327.1679; these data are consistent with that of the racemate prepared by Matthew Earl;[36] enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 208 nm, (*S*)-isomer 22.41 min., (*R*)-isomer 28.93 min.).

5.3.4.2 *N*-alkylation of (*S*)-tert-butyl-3-oxo-2-phenethylpiperazine-1-carboxylate (*S*)-156.



60 % Sodium hydride in mineral oil (100 mg, 2.5 mmol, 2.5 equiv.) in dry THF (8 mL) was stirred at 0 °C for 10 minutes under nitrogen. To this (*S*)-*tert*-butyl-3-oxo-2-phenethylpiperazine-1-carboxylate (*S*)-**156** (304 mg, 1 mmol, 94 % e.e.) in dry THF (4.5 mL) was added dropwise over 10 minutes and left to stir at 0 °C for 90 minutes. Benzyl bromide (0.238 mL, 2 mmol, 2 equiv.) was then added dropwise. The reaction mixture was stirred for a further 10 minutes at 0 °C before being allowed to warm to room temperature where it was stirred for 18 hours. The reaction mixture was quenched with distilled water (10 mL) and extracted with diethyl ether (3 x 20 mL). The organic

extracts were combined and washed with water (30 mL) and brine (30 mL). Organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The yellow oil was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether) to give tert-butyl (*S*)-4-benzyl-3-oxo-2-phenethylpiperazine-1-carboxylate as a yellow solid (*S*)-**157** (197 mg, 50 %).

m.p. 129-130 ºC; ν_{max}/cm^{-1} (neat) 1694 (s, C=O st.), 1649 (s, C=O st.), 1162 (m, N-CO-O st.), 1125 (m, C-N st.), 1004 (w, N-CO-O st.); δ_H (400 MHz; $CDCl_3$) 7.37-7.20 (10H, m, Ar*H*), 4.94 (1H, br. d, *J* 12.5, NC*H*HPh), 4.81-4.68 (1H, br. m, C*H*N), 4.29 (1H, br. d, *J* 13, NCH*H*Ph), 4.22-4.09 (1H, br. m, C*H*HNBoc), 3.42 (1H, td, *J* 11 and 3.5, C*H*HNBn) 3.26-3.16 (1H, m, CH*H*NBoc), 3.15-3.10 (1H, m, CH*H*NBn), 2.83 (1H, td, *J* 13.5 and 5.5, CH_2C*H*HPh), 2.72 (1H, td, *J* 12 and 5, CH_2CH*H*Ph), 2.45-2.36 (1H, m, C*H*HCHCO), 2.11-2.01 (1H, m, CH*H*CHCO), 1.48 (9H, s, 3 x C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 168.5 (*C*O lactam), 154.0 (*C*O Boc), 141.4 (Ar$C_{quat.}$), 136.4 (Ar$C_{quat.}$), 128.8 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.1 (Ar*C*), 127.7 (Ar*C*), 126.0 (Ar*C*), 77.2 (*C*$(CH_3)_3$), 57.3 (C*H*N), 50.0 (N*C*H_2Ph), 45.6 (*C*H_2NBn), 40.8 (*C*H_2NBoc), 34.3 (*C*H_2CHCO), 32.6 (CH_2*C*H_2Ph), 28.3 (3 x *C*H_3); HRMS (ESI) calc. for $C_{24}H_{31}N_2O_3$ ($M+H^+$) 395.2329, found 395.2332; these data are consistent with that of the racemate prepared by Matthew Earl;[36] enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 209 nm, (*R*)-isomer 10.85 min., (*S*)-isomer 13.73 min.).

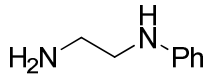
5.3.5 *N*-Arylation of Diamines. General Procedure 8:

Method modified from the literature.[37]

Iodobenzene (2.97 mL, 26.7 mmol, 1 equiv.) and diamine (80 mmol, 3 equiv.) were added *via* syringe to a sealed flask containing CuCl (0.264 g, 2.7 mmol, 0.1 equiv.) and

potassium hydroxide (2.99 g, 53.3 mmol, 2 equiv.) at 0 ºC. The reaction mixture was allowed to warm to 5 °C over 17 hours. The resulting suspension was diluted with water (15 mL) before being extracted with CH_2Cl_2 (4 x 25 mL). Combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the product as an oil.

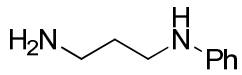
_N_-phenyl-1,2-diaminoethane 160.



The title compound was synthesised using General Procedure 8 with 1,2-ethylenediamine (5.35 mL, 80 mmol) to give a light yellow oil (3.44 g, 95 %).

ν_{max}/cm^{-1} (neat) 3361 (br., NH st.), 3283 (br., NH st.), 1600 (m, NH_2 bend); δ_H (400 MHz; $CDCl_3$) 7.18 (2H, t, *J* 7.5, *m*-Ar*H*), 6.71 (1H, t, *J* 7.5, *p*-Ar*H*), 6.64 (2H, d, *J* 8.5, *o*-Ar*H*), 4.01 (1H, br. s, N*H*Ph), 3.19 (2H, t, *J* 5.5, C*H*$_2$NHPh), 2.96 (2H, t, *J* 6, C*H*$_2$NH$_2$), 1.18 (2H, br. s, N*H*$_2$); δ_C (100 MHz; $CDCl_3$) 148.3 (Ar*C*$_{quat.}$), 129.2 (Ar*C*), 117.4 (Ar*C*), 112.9 (Ar*C*), 46.5 (*C*H$_2$NHPh), 41.2 (*C*H$_2$NH$_2$); HRMS (ESI) calc. for $C_8H_{13}N_2$ (M+H$^+$) 137.1073, found 137.1075. Spectroscopic data are similar to those previously reported.[37]

_N_-phenyl-1,3-diaminopropane 161.



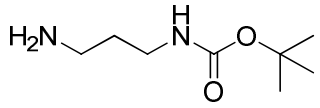
The title compound was synthesised using General Procedure 3 with 1,3-propanediamine (6.68 mL, 80 mmol) to give a light yellow oil (3.56 g, 89 %).

ν_{max}/cm^{-1} (neat) 3352 (br., NH st.), 3292 (br., NH st.), 1600 (m, NH_2 bend); δ_H (400 MHz; $CDCl_3$) 7.17 (2H, t, *J* 7.5, *m*-Ar*H*), 6.69 (1H, t, *J* 7.5, *p*-Ar*H*), 6.62 (2H, d, *J* 8.5, *o*-Ar*H*), 3.89 (1H, br. s, N*H*Ph), 3.19 (2H, t, *J* 7, C*H*$_2$NHPh), 2.85 (2H, t, *J* 7, C*H*$_2$NH$_2$), 1.76 (2H, quin., *J* 7, CH$_2$C*H*$_2$CH$_2$), 1.27 (2H, br. s, N*H*$_2$); δ_C (100 MHz; $CDCl_3$) 148.4 (Ar*C*$_{quat.}$), 129.2 (Ar*C*), 117.1 (Ar*C*), 112.7 (Ar*C*), 42.1 (*C*H$_2$NHPh), 40.63 (*C*H$_2$NH$_2$),

32.9 ($CH_2CH_2CH_2$); HRMS (ESI) calc. for $C_9H_{15}N_2$ ($M+H^+$) 151.1230, found 151.1232. Spectroscopic data are similar to those previously reported.[37]

5.3.6 Synthesis of *N*-Benzylpropane-1,3-diamine 164.

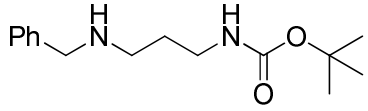
5.3.6.1 *tert*-Butyl (3-aminopropyl)carbamate 162.



To 1,3-diaminopropane (20 mL, 240 mmol, 6 equiv.) in chloroform (36 mL) at 0 °C was added dropwise di-*tert*-butyl dicarbonate (8.73 g, 40 mmol, 1 equiv.) in chloroform (6 mL). The reaction mixture was allowed to warm to room temperature and stirred for a further 3 hours. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and washed with brine (2 x 50 mL). Organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless viscous oil (3.70 g, 53 %), which was used without further purification.

ν_{max}/cm^{-1} (neat) 3350 (br., NH st.), 3167 (br., NH st.), 1686 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 4.94 (1H, br. s, N*H*Boc), 3.19-3.12 (2H, m, C*H*$_2$NHBoc), 2.74 (2H, t, *J* 6.5, C*H*$_2$NH$_2$), 1.58 (2H, pent., $CH_2CH_2CH_2$), 1.41 (9H, s, 3 x C*H*$_3$), 1.28 (2H, br. s, N*H*$_2$); δ_C (100 MHz; $CDCl_3$) 156.1 (*C*O), 77.2 (*C*$(CH_3)_3$), 39.7 (*C*H_2NH_2), 38.4 (*C*H_2NHBoc), 33.4 ($CH_2CH_2CH_2$), 28.4 (3 x *C*H_3); HRMS (ESI) calc. for $C_8H_{19}N_2O_2$ ($M+H^+$) 175.1441, found 175.1438. Spectroscopic data are similar to those previously reported.[38]

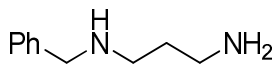
5.3.6.2 *tert*-Butyl (3-(benzylamino)propyl)carbamate 163.



To a solution of *tert*-butyl (3-aminopropyl)carbamate **162** (3.65 g, 21 mmol, 1 equiv.) in methanol (75 mL) and triethylamine (2.93 mL, 21 mmol, 1 equiv.) at 0 ºC was added benzaldehyde (2.14 mL, 21 mmol, 1 equiv.). The reaction mixture was allowed to warm to room temperature where it was stirred for a further 3 hours before being cooled to 0 °C. Sodium borohydride (1.59 g, 42 mmol, 2 equiv.) was added portionwise and the reaction mixture was stirred at 0 °C for 1 hour before being neutralised with 2 M hydrochloric acid. Organics were removed *in vacuo*. Resulting residue was diluted with distilled water (50 mL) and then extracted with ethyl acetate (2 x 50 mL). Combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a green oil (5.39 g, 97 %).

ν_{max}/cm^{-1} (neat) 3340 (br., NH st.), 1687 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.41-7.27 (5H, m, Ar*H*), 5.33 (1H, br. s, N*H*Boc), 3.79 (2H, s, C*H*$_2$Ph), 3.25-3.19 (2H, m, C*H*$_2$NHBoc), 2.73 (2H, t, *J* 6.5, C*H*$_2$NHCH$_2$Ph), 2.01 (1H, br. s, N*H*CH$_2$Ph), 1.73-1.59 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.49 (9H, s, 3 x C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 156.1 (*C*O), 140.0 (ArC$_{quat.}$), 128.5 (Ar*C*), 128.4 (Ar*C*), 127.5 (Ar*C*), 77.2 (*C*(CH$_3$)$_3$), 53.9 (*C*H$_2$Ph), 47.2 (*C*H$_2$NHCH$_2$Ph), 39.3 (*C*H$_2$NHBoc), 29.6 (CH$_2$*C*H$_2$CH$_2$), 28.4 (3 x *C*H$_3$); HRMS (ESI) calc. for $C_{15}H_{25}N_2O_2$ (M+H$^+$) 265.1911, found 265.1913. Spectroscopic data are similar to those previously reported.[38]

5.3.6.3 *N*-Benzylpropane-1,3-diamine 164.



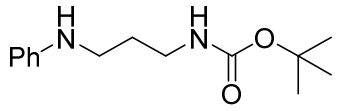
To a solution of *tert*-butyl (3-(benzylamino)propyl)carbamate **163** (5.30 g, 20 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) at 5 °C was added dropwise trifluoroacetic acid (10 mL) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to warm to room temperature where it was stirred for a further 6 hours. Reaction mixture was concentrated *in vacuo*, diluted

with distilled water (10 mL) and the pH was adjusted to 14 with 4 M sodium hydroxide. Resulting solution was extracted with CH_2Cl_2 (3 x 30 mL). Combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (3.21 g, 97 %), which was used without further purification.

δ_H (400 MHz; $CDCl_3$) 7.24-7.35 (5H, m, Ar*H*), 3.78 (2H, s, C*H*$_2$Ph), 2.75 (2H, t, *J* 7, C*H*$_2$NHCH$_2$Ph), 2.68 (2H, t, *J* 7, CH_2NH_2), 1.93 (3H, br. s, N*H* and N*H*$_2$), 1.64 (2H, quin., *J* 7, $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 140.0 (Ar*C*$_{quat.}$), 128.4 (Ar*C*), 128.1 (Ar*C*), 127.5 (Ar*C*), 54.0 (*C*H$_2$Ph), 47.3 (C*H*$_2$NHCH$_2$Ph), 40.5 (*C*H$_2$NH$_2$), 33.1 ($CH_2CH_2CH_2$); HRMS (ESI) calc. for $C_{10}H_{17}N_2$ ($M+H^+$) 165.1386, found 166.1420. Spectroscopic data are similar to those previously reported.[39]

5.3.7 Synthesis of *N*^{1}-Benzyl-*N*^{1}-Phenylpropane-1,3-diamine 185.

5.3.7.1 *tert*-Butyl (3-(phenylamino)propyl)carbamate 183.

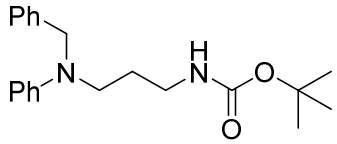


To *N*-phenyl-1,3-diaminopropane **161** (3.16 g, 21.1 mmol, 1 equiv.) in methanol (60 mL) was added dropwise di-*tert*-butyl dicarbonate (4.69 g, 21.5 mmol, 1.02 equiv.) in methanol (24 mL) and resulting solution stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether to 40 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (4.06 g, 77 %).

ν_{max}/cm^{-1} (neat) 3367 (br., NH st.), 1688 (s, C=O st.); δ_H (300 MHz; $CDCl_3$) 7.20-7.14 (2H, m, Ar*H*), 6.70 (1H, t, *J* 7.5, *p*-Ar*H*), 6.61 (2H, d, *J* 8, Ar*H*), 4.68 (1H, br. s, N*H*Boc), 3.81 (1H, br. s, N*H*Ph), 3.23 (2H, q, *J* 6.5, C*H*$_2$NHBoc), 3.18 (2H, t, *J* 6.5, C*H*$_2$NHPh), 1.78 (2H, quin. J 6.5, C*H*$_2$CH$_2$NHPh), 1.45 (9H, m, 3 x C*H*$_3$); δ_C (75 MHz;

$CDCl_3$) 156.2 (*C*O), 148.0 (Ar$C_{quat.}$), 129.2 (Ar*C*), 117.3 (Ar*C*), 112.9 (Ar*C*), 79.3 (*C*$(CH_3)_3$), 41.0 (*C*H_2), 38.1 (*C*H_2), 29.6 (*C*H_2), 28.4 (3 x *C*H_3); HRMS (ESI) calc. for $C_{14}H_{23}N_2O_2$ ($M+H^+$) 251.1754, found 251.1757.

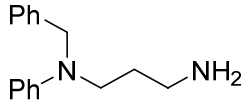
5.3.7.2 *tert*-Butyl (3-(benzyl(phenyl)amino)propyl)carbamate 184.



To *tert*-Butyl (3-(benzylamino)propyl)carbamate **183** (2.36 g, 9.4 mmol, 1 equiv.) and potassium carbonate (1.96 g, 14.2 mmol, 1.5 equiv.) in ethanol (38 mL) was added benzyl bromide (1.68 mL, 14.2 mmol, 1.5 equiv.). The resulting mixture was heated to reflux for 3 hours before being allowed to cool to room temperature. Reaction mixture was concentrated *in vacuo* and partitioned between distilled water (40 mL) and ethyl acetate (3 x 30 mL). Combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether to 10 % ethyl acetate in 40-60 petroleum ether) to give a light yellow oil (1.91 g, 60 %).

ν_{max}/cm^{-1} (neat) 3354 (br., NH st.), 1692 (s, C=O st.); δ_H (300 MHz; $CDCl_3$) 7.62-7.29 (7H, m, Ar*H*), 6.91-6.78 (3H, m, Ar*H*), 4.71-4.63 (3H, m, CH_2Ph and N*H*Boc), 3.57 (2H, t, *J* 7.5, CH_2NPh), 3.31 (2H, br. q, *J* 7, CH_2NHBoc), 1.98 (2H, quin., *J* 7, $CH_2CH_2CH_2$), 1.58 (9H, s, 3 x CH_3); δ_C 129.2 (Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 126.6 (Ar*C*), 116.5 (Ar*C*), 112.5 (Ar*C*), 69.4 (*C*H_2), 64.1 (*C*H_2), 54.8 (*C*H_2), 48.5 (*C*H_2), 28.3 (3 x *C*H_3); HRMS (ESI) calc. for $C_{21}H_{29}N_2O_2$ ($M+H^+$) 341.2224, found 341.2222. Four quarternary peaks peaks in the ^{13}C NMR spectrum were not resolvable; *C*O, 2 x Ar$C_{quat.}$ and *C*(CH3)3.

5.3.7.3 N^1-Benzyl-N^1-phenylpropane-1,3-diamine 185.



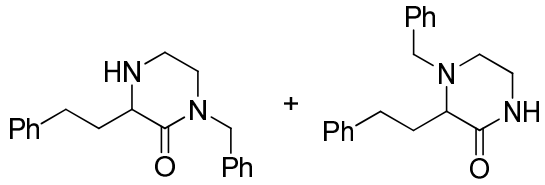
To a solution of *tert*-butyl (3-(benzyl(phenyl)amino)propyl)carbamate **184** (1.98 g, 5.82 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) at 5 °C was added dropwise trifluoroacetic acid (5 mL) in CH_2Cl_2 (20 mL). The reaction mixture was allowed to warm to room temperature where it was stirred for a further 6 hours. Reaction mixture was concentrated *in vacuo*, diluted with distilled water (10 mL) and the pH was adjusted to 14 with 4 M sodium hydroxide. Resulting solution was extracted with CH_2Cl_2 (3 x 30 mL). Combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (0.55 g, 39 %), which was used without further purification.

ν_{max}/cm^{-1} (neat) 3304 (br., NH_2 st.), 1596 (m, NH_2 bend), 1503 (m, C-N st.); δ_H (250 MHz; $CDCl_3$) 7.34-7.13 (7H, m, Ar*H*), 6.76-6.59 (3H, m, Ar*H*), 4.55 (2H, s, C*H*$_2$Ph), 3.52-3.41 (2H, m, CH_2N), 2.77 (2H, t, *J* 7, CH_2N), 1.81 (2H, quin., *J* 7, $CH_2CH_2CH_2$), 1.33 (2H, br. s, NH_2); δ_C (75 MHz; $CDCl_3$) 148.5 (Ar*C*$_{quat.}$), 138.9 (Ar*C*$_{quat.}$), 128.5 (Ar*C*), 126.7 (Ar*C*), 126.5 (Ar*C*), 116.2 (Ar*C*), 112.7 (Ar*C*), 112.3 (Ar*C*), 54.5 (CH_2), 48.7 (CH_2), 40.0 (CH_2), 31.1 (CH_2); HRMS (ESI) calc. for $C_{16}H_{21}N_2$ ($M+H^+$) 241.1699, found 241.1704.

5.3.8 Jocic-type Reactions with Unsymmetrical Diamines.

5.3.8.1 Racemic Products.

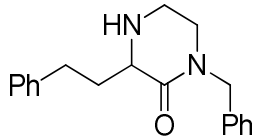
1-Benzyl-3-phenethylpiperazin-2-one 158 and 4-benzyl-3-phenethylpiperazin-2-one 159.



The title compounds were synthesised in a 86 : 14 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-benzyl-1,2-ethylenediamine (0.75 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give 1-benzyl-3-phenethylpiperazin-2-one **158** as a yellow solid (230 mg, 78 %) and 4-benzyl-3-phenethylpiperazin-2-one **159** as a yellow solid (14 mg, 5 %).

Individual characterisation data:

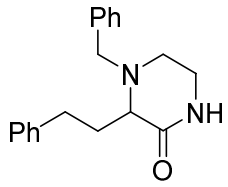
1-Benzyl-3-phenethylpiperazin-2-one 158.



m.p. 58-61 ºC; ν_{max}/cm^{-1} (neat) 3328 (br. m, NH st.), 1629 (s, C=O st.), 1227 (s, C-N st.); δ_H (400 MHz; $CDCl_3$) 7.36-7.17 (10H, m, Ar*H*), 4.64 (1H, d, *J* 14.5, NC*H*HPh), 4.57 (1H, d, *J* 14.5, NCH*H*Ph), 3.51 (1H, dd, *J* 8.5 and 4, C*H*N), 3.31 (1H, ddd, *J* 11.5, 8.5 and 4.5, C*H*HNBn), 3.16-3.13 (1H, m, C*H*HNH), 3.10-3.06 (1H, m, CH*H*NBn), 2.95 (1H, ddd, *J* 13.5, 10.5 and 5, CH*H*NH), 2.85-2.71 (2H, m, CH_2CH_2Ph), 2.37 (1H, dddd, *J* 14, 10.5, 7 and 4, C*H*HCHCO), 2.03 (1H, dddd, *J* 14, 9.5, 8.5 and 6, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 171.2 (*C*O), 141.6 ($(CH_2)_2ArC_{quat.}$), 136.9

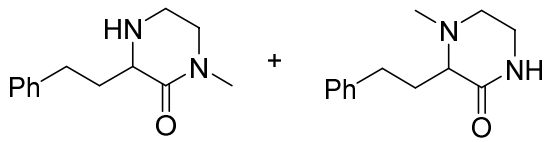
(NCH$_2$Ar*C*$_{quat.}$), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.9 (Ar*C*), 58.7 (*C*HN), 50.1 (N*C*H$_2$Ph), 47.6 (*C*H$_2$NBn), 41.7 (*C*H$_2$NH), 34.1 (*C*H$_2$CHCO), 32.3 (CH$_2$*C*H$_2$Ph); HRMS (ESI) calc. for $C_{19}H_{23}N_2O$ (M+H$^+$) 295.1805, found 295.1807.

4-Benzyl-3-phenethylpiperazin-2-one 159.



m.p. 125-127 ºC; ν_{max}/cm^{-1} (neat) 3201 (br., NH st.), 1666 (s, C=O st.), 1494 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.28-7.04 (10H, m, Ar*H*), 6.73 (1H, br. s, N*H*), 3.89 (1H, d, *J* 13.5, NC*H*HPh), 3.33 (1H, d, *J* 13.5, NCH*H*Ph), 3.24-3.21 (2H, m, C*H*$_2$NH), 3.09 (1H, t, *J* 5, C*H*N), 2.89 (1H, dt, *J* 12.5 and 5, C*H*HNBn), 2.79 (1H, ddd, *J* 14, 11 and 5.5, CH$_2$C*H*HPh), 2.62 (1H, ddd, *J* 13.5, 11 and 5.5, CH$_2$CH*H*Ph), 2.42 (1H, dt, *J* 12.5 and 6, CH*H*NBn), 2.22 (1H, ddt, *J* 14, 11 and 5, C*H*HCHCO), 2.04 (1H, ddt, *J* 14, 10.5 and 5, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 172.4 (*C*O), 142.2 ((CH$_2$)$_2$Ar*C*$_{quat.}$), 138.1 (NCH$_2$Ar*C*$_{quat.}$), 128.8 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 127.3 (Ar*C*), 125.7 (Ar*C*), 64.1 (*C*HN), 58.2 (N*C*H$_2$Ph), 45.0 (*C*H$_2$NBn), 39.9 (*C*H$_2$NH), 32.0 (*C*H$_2$CHCO), 31.4 (CH$_2$*C*H$_2$Ph); HRMS (ESI) calc. for $C_{19}H_{23}N_2O$ (M+H$^+$) 295.1805, found 295.1815.

1-Methyl-3-phenethylpiperazin-2-one 165 and 4-Methyl-3-phenethylpiperazin-2-one 166.

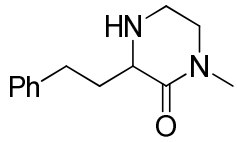


The title compounds were synthesised in a 50 : 50 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-methyl-1,2-

ethylenediamine (0.44 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 10 % MeOH in ethyl acetate) to give 1-methyl-3-phenethylpiperazin-2-one **165** as a yellow oil (103 mg, 47 %) and 4-methyl-3-phenethylpiperazin-2-one **166** as a yellow oil (78 mg, 36 %).

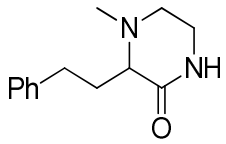
Individual characterisation data:

1-Methyl-3-phenethylpiperazin-2-one 165.



ν_{max}/cm^{-1} (neat) 3429 (br., amine NH st.), 1635 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.32-7.18 (5H, m, Ar*H*), 3.49-3.41 (2H, m, C*H*N and C*H*HNH), 3.24-3.14 (2H, m, CH*H*NH and C*H*HNCH$_3$), 3.07-2.98 (1H, m, CH*H*NCH$_3$), 2.97 (1H, s, NC*H*$_3$), 2.84-2.70 (2H, m, C*H*$_2$Ph), 2.39-2.30 (1H, m, C*H*HCHCO), 2.12 (1H, br. s, N*H*), 1.98 (1H, ddt, *J* 15, 9 and 6, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 170.3 (*C*O), 141.6 (Ar*C*$_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 125.8 (Ar*C*), 58.5 (*C*HN), 50.2 (*C*H$_2$NH), 41.5 (*C*H$_2$NCH$_3$), 34.6 (NCH$_3$), 33.8 (*C*H$_2$CHCO), 32.3 (*C*H$_2$Ph); HRMS (ESI) calc. for $C_{13}H_{18}N_2NaO$ (M+Na$^+$) 241.1311, found 241.1317.

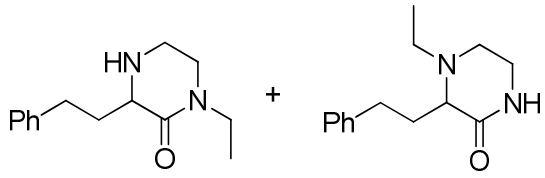
4-Methyl-3-phenethylpiperazin-2-one 166.



ν_{max}/cm^{-1} (neat) 3243 (br., lactam NH st.), 1666 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.29-7.15 (5H, m, Ar*H*), 5.98 (1H, br. s, N*H*), 3.49 (1H, m, C*H*HNH), 3.28 (1H, dq, *J* 11.5 and 3.5, CH*H*NH), 3.00-2.88 (2H, m, C*H*HNCH$_3$ and C*H*N), 2.80 (1H, m, CH*H*CH$_3$), 2.64-2.56 (2H, m, C*H*$_2$Ph), 2.41 (3H, s, C*H*$_3$), 2.31 (1H, dddd, *J* 14, 11.5, 5.5 and 4, C*H*HCHCO), 2.02 (1H, m, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 173.7 (*C*O),

134.4 (Ar$C_{quat.}$), 128.6 (Ar*C*), 128.3 (Ar*C*), 125.7 (Ar*C*), 66.5 (*C*HN), 50.3 (*C*H_2NCH_3), 42.9 (*C*H_3), 40.4 (*C*H_2NH), 31.2 (*C*H_2CHCO), 30.8 (*C*H_2Ph); HRMS (ESI) calc. for $C_{13}H_{18}N_2NaO$ ($M+Na^+$) 241.1311, found 241.1303.

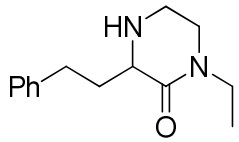
1-Ethyl-3-phenethylpiperazin-2-one 167 and 4-Ethyl-3-phenethylpiperazin-2-one 168.



The title compounds were synthesised in a 75 : 25 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-ethyl-1,2-ethylenediamine (0.53 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 10 % MeOH in ethyl acetate) to give 1-ethyl-3-phenethylpiperazin-2-one **167** as a light yellow oil (169 mg, 72 %) and 4-ethyl-3-phenethylpiperazin-2-one **168** as a yellow oil (19 mg, 8 %).

Individual characterisation data:

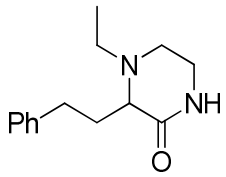
1-Ethyl-3-phenethylpiperazin-2-one 167.



ν_{max}/cm^{-1} (neat) 3457 (br., amine NH st.), 1626 (s, C=O st.); δ_H (600 MHz; $CDCl_3$) 7.30 (2H, t, *J* 7.5, 2 x *o*-Ar*H*), 7.25 (2H, d, *J* 7, 2 x *m*-Ar*H*), 7.20 (1H, t, *J* 7, *p*-Ar*H*), 3.50-3.38 (4H, m, C*H*N, NC*H*$_2$$CH_3$ and C*H*HNC$H_2$$CH_3$), 3.23-3.17 (2H, m, CH*H*NC$H_2$$CH_3$ and C*H*HNH), 3.01 (1H, ddd, *J* 14.5, 11 and 5.5, CH*H*NH), 2.82-2.73 (2H, m, C*H*$_2$Ph), 2.33 (1H, dddd, *J* 14, 10.5, 6.5 and 4, C*H*HCHCO), 1.98 (1H, dtd, *J* 14, 9 and 6, CH*H*CHCO), 1.87 (1H, br. s, N*H*), 1.15 (1H, t, *J* 7, C*H*$_3$); δ_C (150 MHz; $CDCl_3$) 169.6 (*C*O), 141.6 (Ar$C_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 125.8 (Ar*C*), 58.6 (*C*HN), 47.4

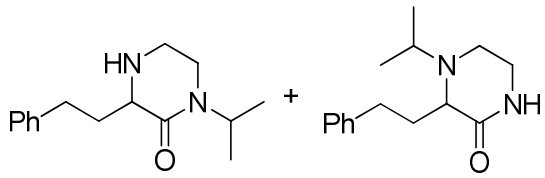
(*C*H_2NCH$_2$CH$_3$), 41.8 (NCH_2CH$_3$), 41.7 (*C*H_2NH), 34.0 (*C*H_2CHCO), 32.2 (*C*H_2Ph), 12.1 (*C*H_3); HRMS (ESI) calc. for $C_{14}H_{21}N_2O$ ($M+H^+$) 233.1648, found 233.1649.

4-Methyl-3-phenethylpiperazin-2-one 168.



v_{max}/cm^{-1} (neat) 3232 (br., lactam NH st.), 1656 (s, C=O st.); δ_H (600 MHz; $CDCl_3$) 7.30 (2H, t, *J* 7, 2 x *m*-Ar*H*), 7.25 (2H, t, *J* 7, 2 x *o*-Ar*H*), 7.20 (1H, t, *J* 7, *p*-Ar*H*), 6.70 (1H, br. s, N*H*), 3.44-3.35 (2H, m, CH_2NH), 3.16-3.10 (2H, m, C*H*N and C*H*HNCH$_2$CH$_3$), 2.83 (1H, ddd, *J* 14, 11 and 5.5, C*H*HPh), 2.81-2.76 (1H, m, NC*H*HCH$_3$), 2.71 (1H, ddd, *J* 13.5, 11 and 5.5, CH*H*Ph), 2.66 (1H, ddd, *J* 12, 7 and 4, CH*H*NCH$_2$CH$_3$), 2.56 (1H, dq, *J* 14 and 7, NCH*H*CH$_3$), 2.23 (1H, ddt, *J* 14, 11 and 5.5, C*H*HCHCO), 2.09 (1H, ddt, *J* 14, 11 and 5, CH*H*CHCO), 1.11 (3H, t, *J* 7, CH_3); δ_C (150 MHz; $CDCl_3$) 172.7 (*C*O), 142.3 (Ar$C_{quat.}$), 128.5 (Ar*C*), 128.2 (Ar*C*), 125.7 (Ar*C*), 63.4 (*C*HN), 47.4 (NCH_2CH$_3$), 44.7 (*C*H_2NCH$_2$CH$_3$), 39.8 (*C*H_2NH), 31.8 (*C*H_2CHCO), 31.5 (*C*H_2Ph), 11.9 (*C*H_3); HRMS (ESI) calc. for $C_{14}H_{20}N_2NaO$ ($M+Na^+$) 255.1468, found 255.1470.

1-Isopropyl-3-phenethylpiperazin-2-one 169 and 4-isopropyl-3-phenethylpiperazin-2-one 170.

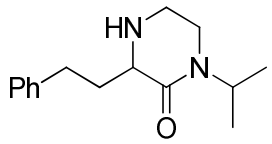


The title compounds were synthesised in a 95 : 5 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-isopropyl-1,2-ethylenediamine (0.62 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 5 % MeOH in ethyl acetate) to give 1-

isopropyl-3-phenethylpiperazin-2-one **169** as a colourless oil (157 mg, 64 %) and 4-isopropyl-3-phenethylpiperazin-2-one **170** as a light yellow oil (4 mg, 2 %).

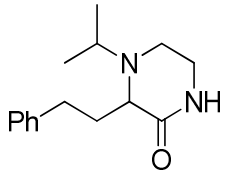
Individual characterisation data:

1-Isopropyl-3-phenethylpiperazin-2-one 169.



ν_{max}/cm^{-1} (neat) 3304 (br., amine NH st.), 1620 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.31-7.17 (5H, m, Ar*H*), 4.89 (1H, sept., *J* 7, C*H*$(CH_3)_2$), 3.44 (1H, dd, *J* 8.5 and 3.5, C*H*NH), 3.30-3.13 (3H, m, C*H*HNH, C*H*HNCH$(CH_3)_2$ and CH*H*NCH$(CH_3)_2$), 2.99-2.92 (1H, m, CH*H*NH), 2.84-2.72 (2H, m, C*H*$_2$Ph), 2.34 (1H, dddd, *J* 14, 10.5, 7 and 4, C*H*HCHCO), 1.98 (1H, dtd, *J* 15, 9 and 6, CH*H*CHCO), 1.67 (1H, br. s, N*H*), 1.14 (3H, d, *J* 3.5, CH(C*H*$_3$)(CH_3)), 1.12 (1H, d, *J* 3.5, CH(CH_3)(C*H*$_3$)); δ_C (100 MHz; $CDCl_3$) 169.3 (*C*O), 141.7 (Ar*C*$_{quat.}$), 128.5 (Ar*C*), 128.3 (Ar*C*), 125.8 (Ar*C*), 58.8 (*C*HNH), 43.7 (*C*H$(CH_3)_2$), 42.0 (*C*H$_2$NH), 41.0 (*C*H$_2$NCH$(CH_3)_2$), 34.3 (*C*H$_2$CHCO), 32.2 (*C*H$_2$Ph), 19.2 (*C*H$_3$), 19.0 (*C*H$_3$); HRMS (ESI) calc.. for $C_{15}H_{23}N_2O$ ($M+H^+$) 247.1805, found 247.1796.

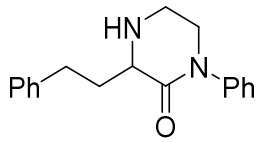
4-Isopropyl-3-phenethylpiperazin-2-one 170.



δ_H (400 MHz; $CDCl_3$) 7.28-7.14 (5H, m, Ar*H*), 5.99 (1H, br. s, N*H*), 3.37-3.27 (3H, m, C*H*NCH$(CH_3)_2$, C*H*HNH and C*H*HNCHC$(CH_3)_2$), 3.08 (1H, sept., *J* 6.5, C*H*$(CH_3)_2$), 2.98 (1H, dt, *J* 12.5 and 4.5, CH*H*NH), 2.79 (1H, ddd, *J* 11.5, 7.5 and 5, C*H*HPh), 2.66-2.59 (2H, m, CH*H*Ph and CH*H*NCH$(CH_3)_2$), 2.26 (1H, dddd, *J* 14, 11.5, 5.5 and 4.5, C*H*HCHCO), 2.05 (1H, ddt, *J* 14, 11 and 5, CH*H*CHCO), 1.13 (3H, d, *J* 6.5,

CH(C*H*$_3$)(CH$_3$)), 0.97 (3H, d, *J* 6.5, CH(CH$_3$)(C*H*$_3$)); δ_C (100 MHz; CDCl$_3$) 172.8 (*C*O), 142.4 (Ar*C*$_{quat.}$), 128.5 (Ar*C*), 128.2 (Ar*C*), 125.7 (Ar*C*), 61.5 (*C*HN), 48.7 (*C*H(CH$_3$)$_2$), 41.2 (*C*H$_2$NCH(CH$_3$)$_2$), 40.0 (*C*H$_2$NH), 32.1 (*C*H$_2$CHCO), 31.1 (*C*H$_2$Ph), 21.6 (*C*H$_3$), 15.1 (*C*H$_3$); HRMS (ESI) calc. for C$_{15}$H$_{23}$N$_2$O (M+H$^+$) 247.1805, found 247.1807.

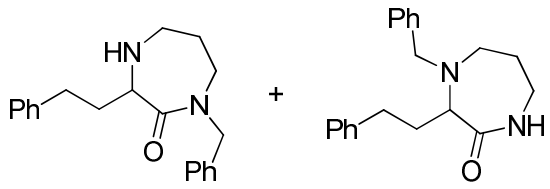
1-Phenyl-3-phenethylpiperazin-2-one 171.



The title compound was synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-phenyl-1,2-ethylenediamine (0.68 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether to ethyl acetate) to give 3-phenethyl-1-phenylpiperazin-2-one **171** as a beige solid (140 mg, 51 %).

m.p. 102-103 ºC; ν_{max}/cm^{-1} (neat) 3294 (br., amine NH st.), 1629 (s, C=O st.); δ_H (400 MHz; CDCl$_3$) 7.41-7.37 (2H, m, Ar*H*), 7.31-7.27 (7H, m, Ar*H*), 7.21-7.16 (1H, m, Ar*H*), 3.81 (1H, ddd, *J* 11.5, 9.5 and 5, C*H*HNH), 3.61 (1H, dd, *J* 8 and 4, C*H*N), 3.57 (1H, dt, *J* 11.5 and 4, CH*H*NH), 3.28 (1H, dt, *J* 13 and 4, C*H*HNPh), 3.17 (1H, ddd, *J* 13.5, 9.5 and 4, CH*H*NPh), 2.89-2.78 (2H, m, C*H*$_2$Ph), 2.37 (1H, dddd, J 16.5, 9.5, 7 and 4, C*H*HCHCO), 2.08 (1H, dtd, *J* 15, 8.5 and 7, CH*H*CHCO), 1.74 (1H, br. s, N*H*); δ_C (100 MHz; CDCl$_3$) 170.1 (*C*O), 142.7 (Ar*C*$_{quat.}$), 141.6 (Ar*C*$_{quat.}$), 129.1 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 126.8 (Ar*C*), 126.0 (Ar*C*), 125.9 (Ar*C*), 59.1 (*C*HN), 51.8 (*C*H$_2$NPh), 42.3 (*C*H$_2$NH), 34.2 (*C*H$_2$CHCO), 32.3 (*C*H$_2$Ph); HRMS (ESI) calc. for C$_{18}$H$_{21}$N$_2$O (M+H$^+$) 281.1648, found 281.1646.

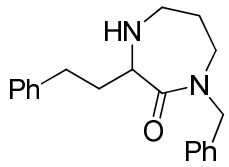
1-Benzyl-3-phenethyl-1,4-diazepan-2-one 172 and 4-benzyl-3-phenethyl-1,4-diazepan-2-one 173.



The title compounds were synthesised in a 73 : 27 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-benzyl-1,3-propylenediamine **161** (0.83 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give 1-benzyl-3-phenethyl-1,4-diazepan-2-one **172** as a colourless oil (147 mg, 48 %) and 4-benzyl-3-phenethyl-1,4-diazepan-2-one **173** as a white solid (27 mg, 9 %).

Individual characterisation data:

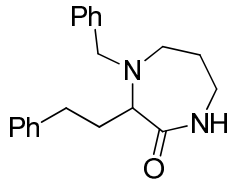
1-benzyl-3-phenethyl-1,4-diazepan-2-one 173.



ν_{max}/cm^{-1} (neat) 3273 (br., NH st.), 1637 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.32-7.15 (10H, m, Ar*H*), 4.68 (1H, d, *J* 14.5, NC*H*HPh), 4.45 (1H, d, *J* 14.5, NCH*H*Ph), 3.47 (1H, dd, *J* 15 and 11.5, C*H*HNCH_2Ph), 3.31-3.19 (3H, m, C*H*N, CH*H*NCH_2Ph and C*H*HNH), 2.86-2.76 (3H, m, CH*H*NH and CH_2C*H*$_2$Ph), 2.24 (1H, dtd, *J* 15.5, 7.5 and 6, C*H*HCHCO), 1.84 (1H, dq, *J* 15 and 7.5, CH*H*CHCO), 1.55-1.41 (1H, m, CH_2C*H*HCH_2), 1.41-1.26 (2H, m, CH_2CH*H*CH_2 and N*H*); δ_C (100 MHz; $CDCl_3$) 175.4 (*C*O), 142.1 (Ar$C_{quat.}$), 137.7 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 127.3 (Ar*C*), 125.7 (Ar*C*), 59.1 (*C*HNH), 51.2 (NCH_2Ph), 50.1 (*C*H_2NH), 47.4

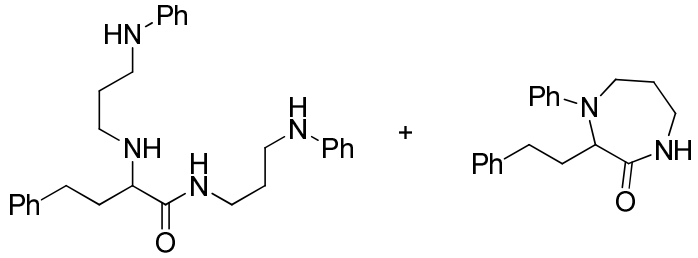
(*C*H_2NCH_2Ph), 34.2 (*C*H_2CHCO), 32.5 (CH_2*C*H_2Ph), 29.8 (CH_2*C*H_2CH_2); HRMS (ESI) calc. for $C_{20}H_{25}N_2O$ ($M+H^+$) 309.1961, found 309.1959.

4-Benzyl-3-phenethyl-1,4-diazepan-2-one 174.



ν_{max}/cm^{-1} (neat) 3250 (br., NH st.), 1666 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.32-7.06 (10H, m, Ar*H*), 5.96 (1H, br. t, *J* 5.5, CON*H*), 3.76 (1H, d, *J* 14, NC*H*HPh), 3.47-3.41 (2H, m, C*H*N and NCH*H*Ph), 3.25 (1H, dddd, *J* 16, 11, 5 and 1, C*H*HNH), 3.20-3.05 (2H, m, CH*H*NH and C*H*HNCH_2Ph), 2.85-2.67 (3H, m, CH_2C*H*$_2$Ph and CH*H*NCH_2Ph), 2.04 (2H, q, *J* 7.5, C*H*$_2$CHCHO), 1.92-1.77 (1H, m, NCH_2*C*H_2), 1.27-1.21 (1H, m, NCH_2CH_2); δ_C (100 MHz; $CDCl_3$) 177.0 (*C*O), 142.2 (Ar*C*$_{quat.}$), 139.3 (Ar*C*$_{quat.}$), 128.7 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.9 (Ar*C*), 125.8 (Ar*C*), 62.8 (*C*HN), 52.2 (*C*H_2NCH_2Ph), 49.7 (N*C*H_2Ph), 41.9 (NH*C*H_2), 32.3 (CH_2*C*H_2Ph), 30.4 (*C*H_2CHCO), 23.0 (NCH_2*C*H_2); HRMS (ESI) calc. for $C_{20}H_{25}N_2O$ ($M+H^+$) 309.1961, found 309.1964.

4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide 181 and 4-phenyl-3-phenethyl-1,4-diazepan-2-one 182.

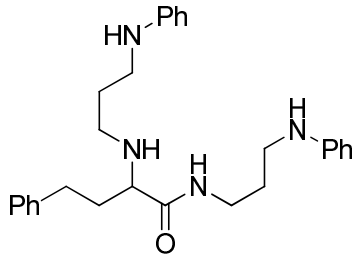


The title compounds were synthesised using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-phenyl-1,3-propanediamine **185** (0.75 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography

(50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give 4-phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide **181** as a colourless oil (221 mg, 50 %) and 4-phenyl-3-phenethyl-1,4-diazepan-2-one **182** as a colourless oil (10 mg, 3 %).

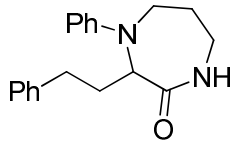
Individual characterisation data:

4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide 181.



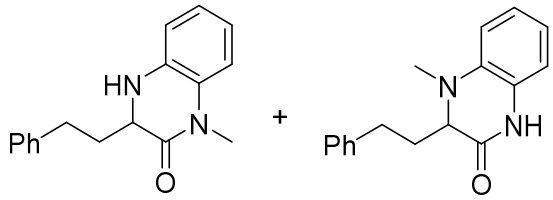
ν_{max}/cm^{-1} (neat) 3324 (br., NH st.), 1600 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.37-7.33 (3H, m, CON*H* and Ar*H*), 7.28-7.21 (7H, m, Ar*H*), 6.79-6.70 (2H, m, Ar*H*), 6.66-6.61 (4H, m, Ar*H*), 3.43-3.30 (2H, m, CONHC*H*$_2$), 3.29-3.12 (5H, m, C*H*N, CHNHC*H*$_2$, CONH(CH$_2$)$_2$C*H*$_2$), 2.82-2.62 (4H, m, C*H*$_2$Ph, CHNH(CH$_2$)$_2$C*H*$_2$), 2.20-2.11 (1H, m, C*H*HCH$_2$Ph), 1.97-1.87 (1H, m, CH*H*CH$_2$Ph), 1.80-1.70 (4H, m, CHNHCH$_2$C*H*$_2$ and CONHCH$_2$C*H*$_2$); δ_C (100 MHz; $CDCl_3$) 174.4 (*C*O), 148.2 (Ar*C*$_{quat.}$), 148.1 (Ar*C*$_{quat.}$), 141.1 (Ar*C*$_{quat.}$), 129.3 (Ar*C*), 129.2 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.1 (Ar*C*), 117.5 (Ar*C*), 117.2 (Ar*C*), 112.8 (Ar*C*), 112.7 (Ar*C*), 63.1 (*C*HN), 46.7 (CHNH(CH$_2$)$_2$*C*H$_2$Ph), 42.1 (CHNH*C*H$_2$), 40.9 (CONH(CH$_2$)$_2$*C*H$_2$), 36.5 (CONH*C*H$_2$), 35.3 (*C*H$_2$CH$_2$Ph), 32.5 (*C*H$_2$Ph), 29.6 (NH$_{amine}$CH$_2$*C*H$_2$), 29.1 (CONHCH$_2$*C*H$_2$); HRMS (ESI) calc. for $C_{28}H_{37}N_4O$ (M+H$^+$) 445.2962, found 445.2957.

4-Phenyl-3-phenethyl-1,4-diazepan-2-one 182.



ν_{max}/cm^{-1} (neat) 3284 (br., NH st.), 1655 (s, C=O st.); δ_H (500 MHz; $CDCl_3$) 7.28-7.14 (7H, m, Ar*H*), 6.89 (2H, d, *J* 8.5, Ar*H*), 6.79 (1H, t, *J* 7.5, Ar*H*), 5.81 (1H, br. t, *J* 4.5,CON*H*), 4.25-4.16 (1H, m, C*H*N), 3.75-3.67 (2H, m, C*H*$_2$NPh), 3.22 (2H, q, *J* 6, CONHC*H*$_2$), 2.77 (1H, ddd, *J* 12, 9 and 4, C*H*HPh), 2.72-2.65 (1H, m, CH*H*Ph), 2.40-2.23 (2H, m, COCHC*H*$_2$), 2.00-1.90 (1H, br. m, NCH$_2$C*H*H), 1.83-1.75 (1H, m, NCH$_2$CH*H*); δ_C (100 MHz; $CDCl_3$) 177.4 (*C*O), 147.7 (Ar*C*$_{quat.}$), 141.4 (Ar*C*$_{quat.}$), 129.4 (Ar*C*), 128.6 (Ar*C*), 128.4 (Ar*C*), 126.0 (Ar*C*), 118.4 (Ar*C*), 114.9 (Ar*C*), 62.4 (*C*HN), 48.0 (*C*H$_2$NPh), 40.9 (CONH*C*H$_2$), 32.4 (*C*H$_2$Ph), 30.8 (COCH*C*H$_2$), 27.0 (NCH$_2$*C*H$_2$); HRMS (ESI) calc. for $C_{19}H_{22}N_2NaO$ (M+Na$^+$) 317.1624, found 317.1628.

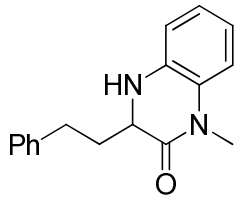
1-Methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one 176 and 4-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one 177.



The title compounds were synthesised in a 78 : 22 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) and *N*-methyl-1,2-phenylenediamine (0.57 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether to 20 % ethyl acetate in 40-60 petroleum ether) to give 1-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one **176** as a yellow oil (140 mg, 53 %) and 4-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one **177** as a red oil (31 mg, 12 %).

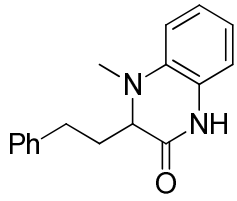
Individual characterisation data:

1-Methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one 176.



ν_{max}/cm^{-1} (neat) 3202 (br., NH st.), 1672 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.22-7.19 (2H, m, Ar*H*), 7.14-7.10 (3H, m, Ar*H*), 6.85-6.80 (2H, m, Ar*H*), 6.77-6.73 (1H, m, Ar*H*), 6.49 (1H, d, *J* 7.5, Ar*H*), 3.82 (1H, dd, *J* 8 and 4.5, C*H*N), 3.77 (1H, br. s, N*H*), 3.27 (3H, s, NC*H*$_3$), 2.77-2.64 (2H, m, C*H*$_2$Ph), 2.09 (1H, dddd, *J* 14, 8.5, 6.5 and 4.5, C*H*HCH$_2$Ph), 1.96-1.86 (1H, m, CH*H*CH$_2$Ph); δ_C (100 MHz; $CDCl_3$) 167.5 (*C*O), 141.0 (Ar*C*$_{quat.}$), 134.3 (Ar*C*$_{quat.}$), 128.8 (Ar*C*$_{quat.}$), 128.6 (Ar*C*), 128.4 (Ar*C*), 126.1 (Ar*C*), 123.5 (Ar*C*), 119.5 (Ar*C*), 114.5 (Ar*C*), 114.3 (Ar*C*), 56.4 (*C*HN), 33.0 (*C*H$_2$CH$_2$Ph), 32.0 (*C*H$_2$Ph), 29.0 (N*C*H$_3$); HRMS (ESI) calc. for $C_{17}H_{18}N_2NaO$ (M+Na$^+$) 289.1311, found 289.1309.

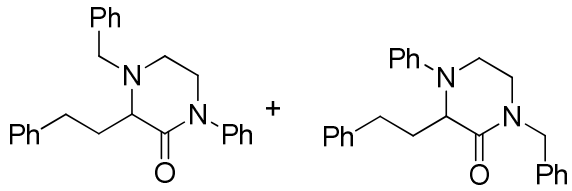
4-Methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one 177.



ν_{max}/cm^{-1} (neat) 3328 (br., NH st.), 1651 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 8.74 (1H, br. s, N*H*), 7.30-7.26 (2H, m, Ar*H*), 7.23-7.14 (3H, m, Ar*H*), 7.06-6.99 (1H, m, Ar*H*), 6.82-6.76 (2H, m, Ar*H*), 6.67 (1H, d, *J* 8, Ar*H*), 3.96 (1H, dd, C*H*N), 2.95 (3H, s, NC*H*$_3$), 2.78-2.66 (2H, m, CH$_2$C*H*$_2$Ph), 2.08-1.87 (2H, m, C*H*$_2$CH$_2$Ph); δ_C (100 MHz; $CDCl_3$) 167.8 (*C*O), 141.1 (Ar*C*$_{quat.}$), 134.8 (Ar*C*$_{quat.}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 126.0 (Ar*C*$_{quat.}$), 125.5 (Ar*C*), 124.3 (Ar*C*), 118.4 (Ar*C*), 115.0 (Ar*C*), 111.9 (Ar*C*), 63.7

(*C*HN), 36.1 (N*C*H_3), 31.7 (*C*H_2Ph), 30.2 (*C*H_2CH_2Ph); HRMS (ESI) Cclc. for $C_{17}H_{18}N_2NaO$ ($M+Na^+$) 289.1311, found 289.1315.

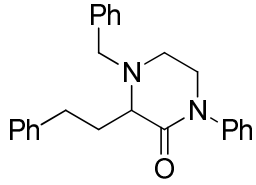
4-Benzyl-3-phenethyl-1-phenylpiperazin-2-one 179 and 1-benzyl-3-phenethyl-4-phenylpiperazin-2-one 180.



The title compounds were synthesised in a 81 : 19 ratio using General Procedure 6 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (254 mg, 1 mmol, 1 equiv.) N^1-benzyl-N^2-phenylethane-1,2-diamine **178** (1.13 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether to 50 % ethyl acetate in 40-60 petroleum ether) to give 4-benzyl-3-phenethyl-1-phenylpiperazin-2-one **179** as a colourless oil (150 mg, 41 %) and 1-benzyl-3-phenethyl-4-phenylpiperazin-2-one **180** as a colourless oil (42 mg, 11 %).

Individual characterisation data:

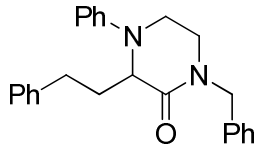
4-Benzyl-3-phenethyl-1-phenylpiperazin-2-one 179.



ν_{max}/cm^{-1} (neat) 1639 (s, C=O st.); δ_H (400 MHz; $CDCl_3$) 7.43-7.16 (15H, m, Ar*H*), 4.09 (1H, d, *J* 13.5, NC*H*HPh), 3.87-3.71 (1H, br. m, C*H*HNPh), 3.57 (1H, dt, *J* 12 and 4, CH*H*NPh), 3.45 (1H, d, *J* 13.5, NCH*H*Ph), 3.40 (1H, t, *J* 4.5, C*H*N), 3.19-3.08 (1H, br. m, C*H*HNCH_2Ph), 3.00 (1H, ddd, *J* 13.5, 11 and 5, CH_2C*H*HPh), 2.76 (1H, ddd, *J* 13.5, 11 and 5.5, CH*H*CH_2Ph), 2.68 (1H, ddd, *J* 12, 9 and 3, CH*H*NCH_2Ph), 2.55-2.42 (1H, m, C*H*HCH_2Ph), 2.23 (1H, ddt, *J* 16, 10.5 and 5, CH*H*CH_2Ph); δ_C (100 MHz; $CDCl_3$)

169.7 (*C*O), 142.5 (Ar*C*$_{quat.}$), 142.2 (Ar*C*$_{quat.}$), 138.0 (Ar*C*$_{quat.}$), 129.1 (Ar*C*), 128.8 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 127.4 (Ar*C*), 126.8 (Ar*C*), 125.7 (Ar*C*), 65.2 (*C*HN), 58.6 (NCH_2Ph), 48.9 (*C*H_2NPh), 46.4 (*C*H_2NCH_2Ph), 32.6 (*C*H_2CH_2Ph), 31.4 (CH_2*C*H_2Ph); HRMS (ESI) calc. for $C_{25}H_{26}N_2NaO$ (M+Na^+) 393.1937, found 393.1925. One ArC peak in the ^{13}C NMR was not resolable.

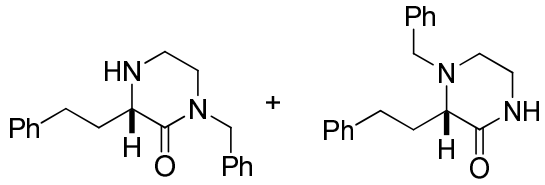
1-Benzyl-3-phenethyl-4-phenylpiperazin-2-one 180.



ν_{max}/cm^{-1} (neat) 1642 (s, C=O st.); δ_H (300 MHz; $CDCl_3$) 7.43-7.21 (12H, m, Ar*H*), 6.89 (1H, t, *J* 7.5, Ar*H*), 6.87-6.78 (2H, m, Ar*H*), 4.87 (1H, d, *J* 14.5, NC*H*HPh), 4.44 (1H, d, *J* 14.5, NCH*H*Ph), 4.37 (1H, t, *J* 6.5, C*H*N), 3.65-3.42 (3H, m, NCH_2 and NC*H*H), 3.28 (1H, dt, *J* 11 and 3, NCH*H*), 2.99-2.81 (2H, m, CH_2CH_2Ph), 2.41-2.15 (2H, m, CH_2CH_2Ph); δ_C (100 MHz; $CDCl_3$) 169.9 (*C*O), 148.4 (Ar*C*$_{quat.}$), 141.5 (Ar*C*$_{quat.}$), 136.6 (Ar*C*$_{quat.}$), 129.4 (Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 128.0 (Ar*C*), 127.6 (Ar*C*), 125.9 (Ar*C*), 119.4 (Ar*C*), 115.5 (Ar*C*), 60.6 (*C*HN), 49.9 (NCH_2Ph), 44.3 (*C*H_2), 42.4 (*C*H_2), 33.6 (*C*H_2CH_2Ph), 32.5 (CH_2*C*H_2Ph); HRMS (ESI) calc. for $C_{25}H_{26}N_2NaO$ (M+Na^+) 393.1937, found 393.1936.

5.3.8.2 Enantiomerically enriched products.

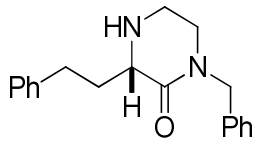
(*S*)-1-Benzyl-3-phenethylpiperazin-2-one (*S*)-158 and (*S*)-4-benzyl-3-phenethyl-piperazin-2-one (*S*)-159.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-benzyl-1,2-ethylenediamine (0.75 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (*S*)-1-benzyl-3-phenethylpiperazin-2-one (*S*)-**158** as a yellow solid (224 mg, 76 %, 95 % e.e.) and (*S*)-4-benzyl-3-phenethylpiperazin-2-one (*S*)-**159** as a yellow solid (18 mg, 6 %, 98 % e.e.).

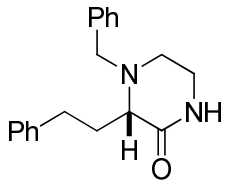
Individual characterisation data:

(*S*)-1-Benzyl-3-phenethylpiperazin-2-one (*S*)-158.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 0.24, $CHCl_3$): - 52.2 (*S*); Enantiomeric excess determined by HPLC analysis on *N*-Boc derivative (*S*)-**157**.

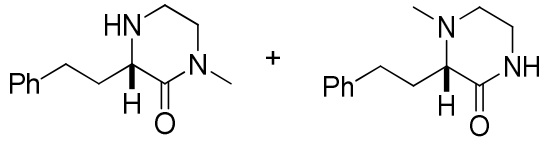
(*S*)-4-Benzyl-3-phenethylpiperazin-2-one (*S*)-158.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 0.28, $CHCl_3$): - 3.0 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-

propanol : hexane = 15 : 85, 1 mL/min., 209 nm, (*R*)-isomer 12.43 min., (*S*)-isomer 14.40 min.).

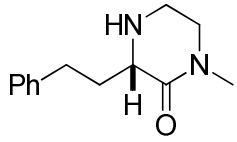
(*S*)-1-Methyl-3-phenethylpiperazin-2-one (*S*)-165 and (*S*)-4-methyl-3-phenethylpiperazin-2-one (*S*)-166.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol ((*R*)-**25**) (254 mg, 1 mmol, 95 % e.e.) and *N*-methyl-1,2-ethylenediamine (0.44 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 10 % MeOH in ethyl acetate) to give (*S*)-1-methyl-3-phenethylpiperazin-2-one (*S*)-**165** as a yellow oil (100 mg, 46 %, 94 % e.e.) and (*S*)-4-methyl-3-phenethylpiperazin-2-one (*S*)-**166** as a yellow oil (89 mg, 41 %, 96 % e.e.).

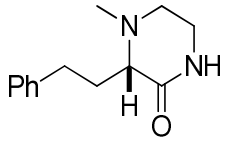
Individual characterisation data:

(*S*)-1-Methyl-3-phenethylpiperazin-2-one (*S*)-165.



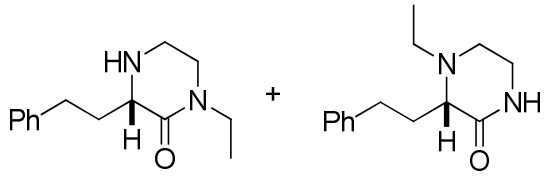
Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.38, $CHCl_3$): - 60.5 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 209 nm, (*S*)-isomer 24.30 min., (*R*)-isomer 27.84 min.).

(*S*)-4-Methyl-3-phenethylpiperazin-2-one (*S*)-166.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.66, $CHCl_3$): - 7.1 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 209 nm, (*S*)-isomer 12.64 min., (*R*)-isomer 23.53 min.).

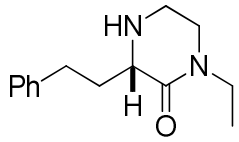
(*S*)-1-ethyl-3-phenethylpiperazin-2-one (*S*)-167 and (*S*)-4-ethyl-3-phenethylpiperazin-2-one (*S*)-168.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-ethyl-1,2-ethylenediamine (0.53 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 10 % MeOH in ethyl acetate) to give (*S*)-1-ethyl-3-phenethylpiperazin-2-one (*S*)-**167** as a yellow oil (168 mg, 72 %, 96 % e.e.) and (*S*)-4-ethyl-3-phenethylpiperazin-2-one (*S*)-**168** as a yellow oil (12 mg, 5 %, 95 % e.e.).

Individual characterisation data:

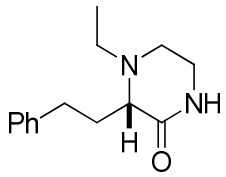
(*S*)-1-Ethyl-3-phenethylpiperazin-2-one (*S*)-167.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.52, $CHCl_3$): - 53.6 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-

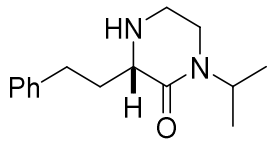
propanol : hexane = 15 : 85, 1 mL/min., 210 nm, (*S*)-isomer 12.85 min., (*R*)-isomer 14.24 min.).

(*S*)-4-Ethyl-3-phenethylpiperazin-2-one (*S*)-168.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{30}$ (c 0.55, $CHCl_3$): + 11.1 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min., 208 nm, (*R*)-isomer 20.63 min., (*S*)-isomer 21.51 min.).

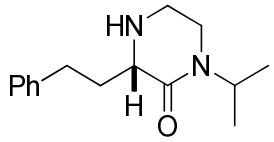
(*S*)-1-Isopropyl-3-phenethylpiperazin-2-one (*S*)-169.



The title compound was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-isopropyl-1,2-ethylenediamine (0.62 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (ethyl acetate to 5 % MeOH in ethyl acetate) to give (*S*)-1-isopropyl-3-phenethylpiperazin-2-one (*S*)-**169** as a yellow oil (168 mg, 72 %, 99 % e.e.).

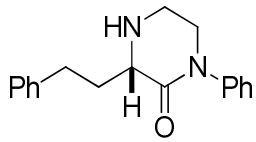
Individual characterisation data:

(*S*)-1-Isopropyl-3-phenethylpiperazin-2-one (*S*)-169.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.38, $CHCl_3$): - 67.1 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 210 nm, (*S*)-isomer 15.20 min., (*R*)-isomer 16.83 min.).

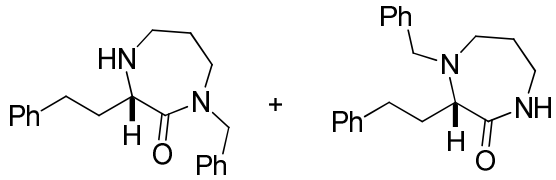
(*S*)-1-Phenyl-3-phenethylpiperazin-2-one (*S*)-171.



The title compound was synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-phenyl-1,2-ethylenediamine **160** (0.68 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to ethyl acetate) to give a colourless oil (145 mg, 52 %, 98 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 0.54, $CHCl_3$): - 57.5 (*S*); Enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 20 : 80, 1 mL/min., 208 nm, (*S*)-isomer 20.09 min., (*R*)-isomer 21.96 min.).

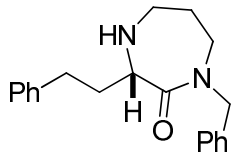
(*S*)-1-Benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-172 and (*S*)-4-benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-173.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-benzyl-1,3-propylenediamine **164** (0.0.83 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (*S*)-1-benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-**172** as a colourless oil (163 mg, 53 %, 99 % e.e.) and 4-benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-**173** as a white solid (35 mg, 11 %, 97 % e.e).

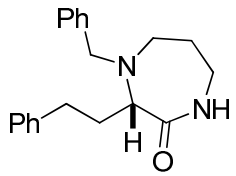
Individual characterisation data:

(*S*)-1-Benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-172.



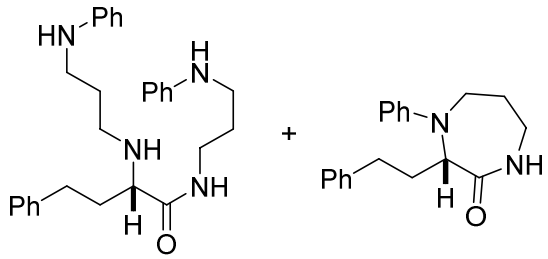
Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 0.27, $CHCl_3$): - 12.0 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 20 : 80, 1 mL/min., 210 nm, (*S*)-isomer 13.23 min., (*R*)-isomer 26.41 min.).

(*S*)-4-Benzyl-3-phenethyl-1,4-diazepan-2-one (*S*)-173.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{30}$ (*c* 0.11, MeOH): - 133.6 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 208 nm, (*S*)-isomer 10.95 min., (*R*)-isomer 13.87 min.).

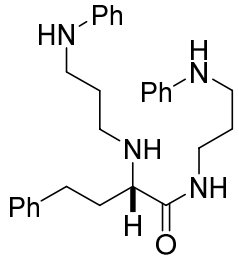
(*S*)-4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide (*S*)-181 and (*S*)-4-phenyl-3-phenethyl-1,4-diazepan-2-one (*S*)-182.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-phenyl-1,3-propanediamine **161** (0.75 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (*S*)-4-phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide (*S*)-**181** as a colourless oil (221 mg, 50 %) and (*S*)-4-phenyl-3-phenethyl-1,4-diazepan-2-one (*S*)-**182** as a colourless oil (10 mg, 3 %, 96 % e.e.).

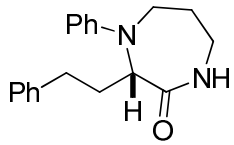
Individual characterisation data:

(*S*)-4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide (*S*)-181.



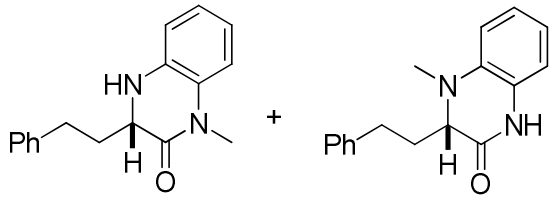
Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{30}$ (*c* 0.89, MeOH): - 4.2 (*S*).

(*S*)-4-Phenyl-3-phenethyl-1,4-diazepan-2-one (*S*)-182.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{30}$ (*c* 0.14, MeOH): + 18.8 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 207 nm, (*R*)-isomer 18.32 min., (*R*)-isomer 33.08 min.).

(*S*)-1-Methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-176 and (*S*)-4-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-177.

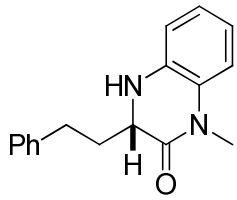


The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and *N*-methyl-1,2-phenylenediamine (0.57 mL, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether to 20 % ethyl

acetate in 40-60 petroleum ether) to give (*S*)-1-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-**176** as a yellow oil (142 mg, 53 %, 96 % e.e.) and (*S*)-4-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-**177** as a red oil (42 mg, 16 %, 98 % e.e.).

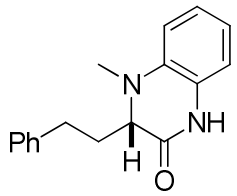
Individual characterisation data:

(*S*)-1-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-176.



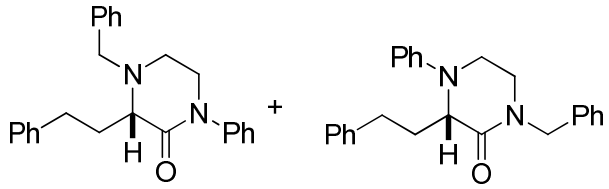
Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.86, MeOH): + 54.8 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 222 nm, (*S*)-isomer 21.39 min., (*R*)-isomer 31.64 min.).

(*S*)-4-methyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (*S*)-177.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{28}$ (*c* 0.24, MeOH): + 131.5 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 222 nm, (*S*)-isomer 14.12 min., (*S*)-isomer 33.82 min.).

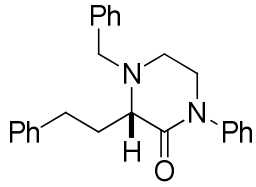
(*S*)-4-benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-179 and (*S*)-1-benzyl-3-phenethyl-4-phenylpiperazin-2-one (*S*)-180.



The title compounds were synthesised using General Procedure 6 with (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and N^1-benzyl-N^2-phenylethane-1,2-diamine **178** (1.13 g, 5 mmol, 5 equiv.). The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether) to give (*S*)-4-benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-**179** as a colourless oil (140 mg, 38 %, 94 % e.e.) and (*S*)-1-benzyl-3-phenethyl-4-phenylpiperazin-2-one (*S*)-**180** as a colourless oil (26 mg, 7 %, 95 % e.e.).

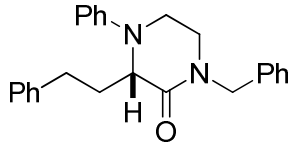
Individual characterisation data:

(*S*)-4-benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-179.



Spectroscopic data similar to that of racemate; $[\alpha]_D^{25}$ (*c* 0.26, MeOH): - 27.9 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 15 : 85, 1 mL/min., 208 nm, (*S*)-isomer 17.96 min., (*R*)-isomer 31.45 min.).

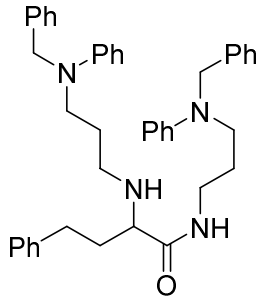
(*S*)-1-benzyl-3-phenethyl-4-phenylpiperazin-2-one (*S*)-180.



Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{25}$ (*c* 0.12, MeOH): + 54.6 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 15 : 85, 1 mL/min., 209 nm, (*R*)-isomer 13.87 min., (*S*)-isomer 20.27 min.).

5.3.9 Independent Synthesis and Isolation of 4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl)butanamide 181.

5.3.9.1 4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl) butanamide 186.

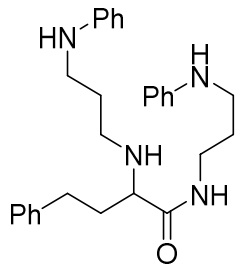


The title compound was synthesised using General Procedure 1 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (182 mg, 0.72 mmol, 1 equiv.) and N^1-phenyl-N^1-benzyl-1,3-propanediamine (864 mg, 3.6 mmol, 5 equiv.). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether to 20 % ethyl acetate in petroleum ether) to afford a colourless oil (85 mg, 19 %).

ν_{max}/cm^{-1} (neat) 3324 (br., NH st.), 1598 (s, C=O st.); δ_H (300 MHz; $CDCl_3$) 7.33-7.14 (19H, m, Ar*H*), 7.04 (1H, t, *J* 5.5, CON*H*), 6.73-6.63 (6H, m, Ar*H*), 4.50 (2H, s, NC*H*$_2$Ph), 4.48 (2H, s, NC*H*$_2$Ph), 3.41-3.18 (6H, m, 3 x C*H*$_2$), 2.99 (1H, dd, *J* 7.5 and 5,

C*H*NH), 2.73-2.60 (2H, m, CH_2CH_2Ph), 2.56-2.43 (2H, m, CHNHCH_2), 2.06-1.97 (1H, m, COCHC*H*H), 1.85-1.76 (3H, m, COCHCH*H* and $CH_2CH_2CH_2$), 1.74-1.64 (2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 174.5 (*C*O), 148.5 (Ar$C_{quat.}$), 148.4 (Ar$C_{quat.}$), 141.1 (Ar$C_{quat.}$), 138.73 (Ar$C_{quat.}$), 138.69 (Ar$C_{quat.}$), 129.3 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.8 (Ar*C*), 126.58 (Ar*C*), 126.56 (Ar*C*), 126.1 (Ar*C*), 116.6 (Ar*C*), 116.5 (Ar*C*), 112.5 (Ar*C*), 112.4 (Ar*C*), 63.2 (*C*HN), 54.7 (CH_2), 54.5 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 46.6 (NHCHCH_2), 36.8 (CH_2), 35.2 (COCHCH_2), 32.5 (CH_2CH_2Ph), 27.9 ($CH_2CH_2CH_2$), 27.5 ($CH_2CH_2CH_2$); HRMS (ESI) calc. for $C_{42}H_{49}H_4O$ ($M+H^+$) 625.3901, found 625.3907. Three of the Ar*C* peaks in the ^{13}C NMR spectrum were not resolvable.

5.3.9.2 4-Phenyl-*N*-(3-phenylamino)propyl)-2-((3-(phenylamino)propyl) butanamide 181.



To a suspension of Pd/C (20 mg) in methanol (10 mL) was added **186** (54 mg, 0.09 mmol, 1 equiv.) and ammonium formate (57 mg, 0.9 mmol, 10 equiv.) and was heated to reflux for 3 hours. Reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue was extracted with ethyl acetate (3 x 15 mL) and water (15 mL). Organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a colourless oil (25 mg, 60 %).

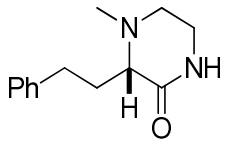
Spectroscopic data similar to that of (*S*)-**181**.

5.3.10 *N*-Amino Alkylation of (*S*)-140, (*S*)-171 and 153. General Procedure 9:

Method modified from the literature.[40]

To a solution of (*S*)-3-phenethylpiperazin-2-one (*S*)-**140** (205 mg, 1 mmol, 1 equiv.) in acetonitrile (13 mL) was added K_2CO_3 (275 mg, 2 mmol, 2 equiv.) and then alkylating agent (1.05 mmol, 1.05 equiv.). The reaction mixture was stirred at 55 ºC for 17 hours. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (25 mL) and washed with water (2 x 30 mL). Organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography.

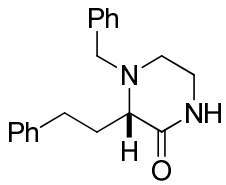
(*S*)-4-Methyl-3-phenethylpiperazin-2-one (*S*)-166.



The title compound was synthesised using General Procedure 9 with (*S*)-3-phenethylpiperazin-2-one (*S*)-**140** (205 mg, 1 mmol, 95 % e.e.) and methyl iodide (19.5 µL, 1.05 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to ethyl acetate) to give a yellow oil (80 mg, 37 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_D^{26}$ (*c* 0.58, $CHCl_3$): - 5.3 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 209 nm, (*S*)-isomer 13.29 min., (*R*)-isomer 24.78 min.).

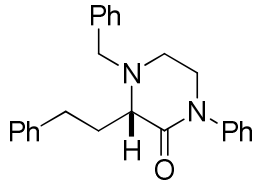
(*S*)-4-Benzyl-3-phenethylpiperazin-2-one (*S*)-159.



The title compound was synthesised using General Procedure 9 with (*S*)-3-phenethylpiperazin-2-one (*S*)-**159** (205 mg, 1 mmol, 95 % e.e.) and benzyl bromide (125 µL, 1.05 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to ethyl acetate) to give a yellow solid (171 mg, 58 %, 95 % e.e.).

Spectroscopic data similar to that of racemate; $[\alpha]_{D}^{26}$ (*c* 0.30, $CHCl_3$): - 6.6 (*S*); enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 15 : 85, 1 mL/min., 209 nm, (*R*)-isomer 12.32 min., (*R*)-isomer 14.09 min.).

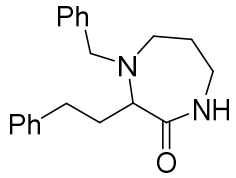
(*S*)-4-Benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-179.



The title compound was synthesised using General Procedure 9 with (*S*)-1-phenyl-3-phenethylpiperazin-2-one (*S*)-**171** (16 mg, 0.06 mmol, 98 % e.e.) with benzyl bromide (7.5 µL, 0.063 mmol). The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to ethyl acetate) to give a yellow oil (11 mg, 50 %, 98 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 208 nm, (*S*)-isomer 18.65 min., (*R*)-isomer 32.26 min.).

4-Benzyl-3-phenethyl-1,4-diazepan-2-one 173.

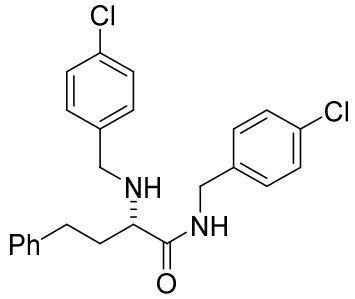


The title compound was synthesised using General Procedure 9 with 3-phenethyl-1,4-diazepan-2-one **153** (20 mg, 0.09 mmol) and benzyl bromide (12 µL, 0.1 mmol). The ^{1}H NMR of the crude residue was consistent with that isolated from the Jocic-type reaction.

5.3.11 Synthesis of Amino-amides using Methanol and NaOH. General Procedure 10:

To (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** (254 mg, 1 mmol, 95 % e.e.) and amine (5 mmol, 5 quiv.) in methanol (4 mL) was added base (5 mmol, 5 equiv.) and resulting mixture stirred at stated temperature for 20 hours. Reaction mixture was cooled and concentrated *in vacuo*. Residue was taken up in ethyl acetate (15 mL) and washed with water (15 mL). Aqueous layer was extracted a further two times with ethyl acetate (2 x 15 mL). Combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Residue was purified by silica column chromatography.

(*S*)-*N*-(4-Chlorobenzyl)-2-((4-chlorobenzyl)amino)-4-phenylbutanamide (*S*)-147.

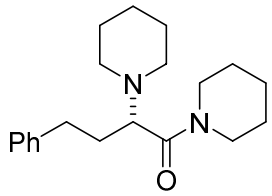


The title compound was synthesised using General Procedure 10 with 4-chlorobenzylamine (0.61 mL, 5 mmol) and NaOH (200 mg, 5 mmol) at 55 ºC. The residue was purified by silica column chromatography (20 % ethyl acetate in 40-60

petroleum ether to 50 % ethyl acetate in 40-60 petroleum ether) to give a yellow solid (111 mg, 26 %, 88 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min., 217 nm, (*S*)-isomer 19.32 min., (*R*)-isomer 24.24 min.).

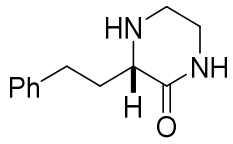
(*S*)-4-Phenyl-1,2-di(piperidin-1-yl)butan-1-one (*S*)-152.



The title compound was synthesised using General Procedure 10 with piperidine (0.49 mL, 5 mmol) and NaOH (200 mg, 5 mmol) at 55 ºC. The residue was purified by silica column chromatography (ethyl acetate) to give a colourless oil (116 mg, 37 %, 96 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95, 0.5 mL/min., 212 nm, (*R*)-isomer 8.31 min., (*S*)-isomer 10.29 min.).

(*S*)-3-phenethylpiperazin-2-one (*S*)-140.



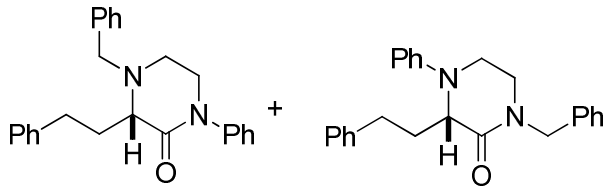
The title compound was synthesised using General Procedure 10 with 1,2-diaminoethane (0.67 mL, 10 mmol) and NaOH (200 mg, 5 mmol) at 55 ºC. The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % MeOH in CH_2Cl_2) to give a yellow solid (92 mg, 45 %, 54 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 50 : 50, 0.5 mL/min., 210 nm, (*S*)-isomer 13.13 min., (*R*)-isomer 16.24 min.).

The title compound was synthesised using General Procedure 10 with 1,2-diaminoethane (0.67 mL, 10 mmol) and 25 % sodium methoxide in methanol (1.14 mL, 5 mmol) at room temperature. The residue was purified by silica column chromatography (CH_2Cl_2 to 20 % MeOH in CH_2Cl_2) to give a yellow solid (66 mg, 32 %, 91 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 50 : 50, 0.5 mL/min., 210 nm, (*S*)-isomer 12.72 min., (*R*)-isomer 15.48 min.).

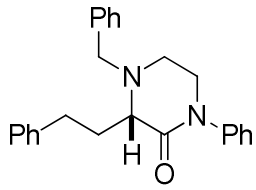
(*S*)-4-Benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-179 and (*S*)-1-benzyl-3-phen-ethyl-4-phenylpiperazin-2-one (*S*)-180.



The title compounds were synthesised using General Procedure 10 with N^1-phenyl-N^2-benzyl-1,2-ethylenediamine (1.13 g, 5 mmol) and NaOH (200 mg, 5 mmol) at 55 ºC. The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether to 50 % ethyl acetate in 40-60 petroleum ether) to give (*S*)-4-benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-**179** as a colourless oil (104 mg, 28 %, 91 % e.e.) and (*S*)-1-benzyl-3-phenethyl-4-phenylpiperazin-2-one (*S*)-**180** as a colourless oil (37 mg, 10 %, 84 % e.e.).

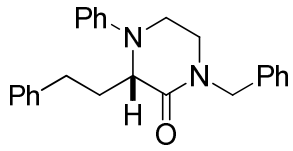
Individual data:

(*S*)-4-Benzyl-3-phenethyl-1-phenylpiperazin-2-one (*S*)-179.



Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 15 : 85, 1 mL/min., 208 nm, (*S*)-isomer 11.96 min., (*R*)-isomer 25.69 min.).

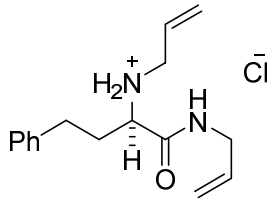
(*S*)-1-Benzyl-3-phenethyl-4-phenylpiperazin-2-one (*S*)-180.



Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Daicel Chiralcel OD-H column, 2-propanol : hexane = 15 : 85, 1 mL/min., 208 nm, (*R*)-isomer 14.56 min., (*S*)-isomer 22.25 min.).

5.3.12 X-ray Crystallographic Data for (*S*)-144.HCl, 146, (*S*)-147, 158, 159 and 171. Performed by Dr Guy J. Clarkson.

5.3.12.1 Crystal structure determination of (*S*)-144.HCl.



To a solution of (*S*)-*N*-allyl-2-(allylamino)-4-phenylbutanamide (*S*)-**144** (26 mg, 0.1 mmol) in CH_2Cl_2 (1 mL), cooled to 5 ^{o}C, was added dropwise 1.0 M HCl in diethyl ether (0.5 mL, 0.5 mmol). The mixture was stirred at 5 °C for 10 minutes and then

allowed to warm to room temperature. After 1 hour the reaction mixture was concentrated *in vacuo* to give a white solid.

Single crystals of (*S*)-**144.HCl** were grown from chloroform/diethyl ether. A suitable crystal was selected and mounted on a glass fibre using Fromblin oil on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,[29] the structure was solved with the ShelXS[33] structure solution program using Direct Methods and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for (*S*)-**144.HCl**: orthorhombic, space group $P2_12_12_1$ (no. 19), a = 4.89752(9) Å, b = 11.8626(2) Å, c = 28.4357(6) Å, V = 1652.05(6) Å^3, Z = 4, T = 150.15 K, μ(Cu Kα) = 2.020 mm^{-1}, *Dcalc* = 1.185 g/mm^3, 5719 reflections measured (6.216 ≤ 2Θ ≤ 154.406), 3358 unique (R_{int} = 0.0216) which were used in all calculations. The final R_1 was 0.0389 (I > 2σ(I)) and wR_2 was 0.1033 (all data).

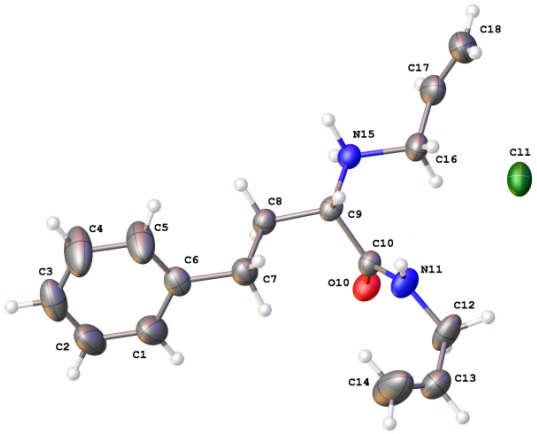
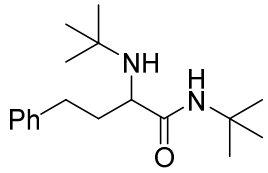


Figure 52 Solid state structure of (*S*)-**144.HCl** with atom labelling. Thermal ellipsoids drawn at 50 % probability.

The asymmetric unit contains the amino acid hydrochloride salt. The unit cell contains four equivalents of **(*S*)-144.HCl**. The hydrogens on N11 and N15 were located in a difference map and refined with a DFIX restraint and given thermal parameters U_{iso} 1.5 times the U_{equiv} of the parent nitrogen atom. The Flack parameter refined to 0.011(11)

from 1198 selected quotients (Parsons' method).[34] The Hooft y parameter refined to 0.009(10) (Olex2).[29]

5.3.12.2 Crystal structure determination of 146.



Single crystals of **146** were grown from ethyl acetate/hexane. A suitable crystal was selected and mounted on a glass fibre with Fromblin on an Oxford Diffraction Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 120(2)K during data collection. Using Olex2,[29] the structure was solved with the ShelXS[33] structure solution program using Direct Methods and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for **146**: orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.17114(12) Å, b = 12.3956(2) Å, c = 24.5886(4) Å, V = 1880.91(6) Å^3, Z = 4, T = 123.15 K, μ(Cu Kα) = 0.487 mm^{-1}, *Dcalc* = 1.026 g/mm^3, 16534 reflections measured ($7.19 \leq 2\Theta \leq 133.184$), 3324 unique ($R_{int}$ = 0.0482) which were used in all calculations. The final R_1 was 0.0613 ($I > 2\sigma(I)$) and wR_2 was 0.1608 (all data).

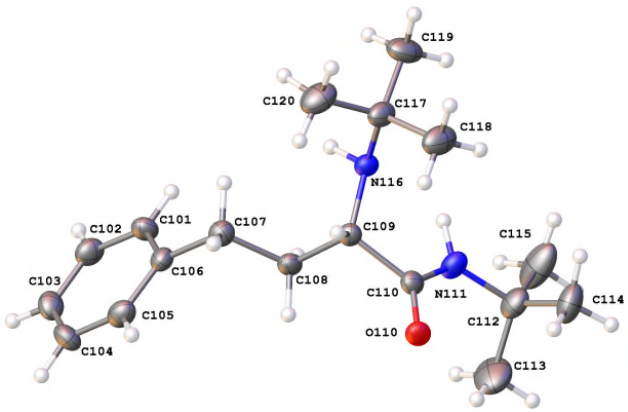
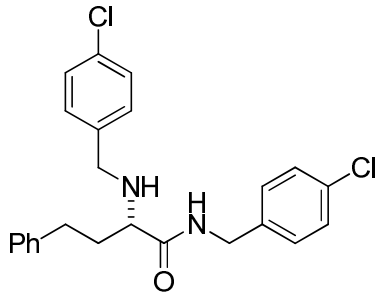


Figure 53 Major rotamer in the solid state structure of **146** with atom labelling. Thermal ellipsoids are drawn at 50 % probability.

The original refinement had a high R factor (16%). A minor component occupying the same position was detected. This is the same molecule with a slightly different orientation. The molecule was refined as disordered over two positions (total molecule disorder). These two orientations are chemically identical (same stereochemistry) and only differ in the orientation of the molecule. The occupancy of the two isomers was linked to a free variable which refined to 82 : 18. The minor component was refined isotropically. The NH on N116 and N216 were located in a difference map. They were allowed to refine with a DFIX restraint and given thermal parameter equivalent to 1.5 times the equivalent Uiso of N116 or N216. The NHs on N111 and N211 were placed at calculated positions.

5.3.12.3 Crystal Structure Determination of (*S*)-147.



Single crystals of **(*S*)-147** were grown from benzene/hexane. A suitable crystal was selected and mounted on a glass fibre using Fromblin oil on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,[29] the structure was solved with the Superflip[30-32] structure solution program using Charge Flipping and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for (*S*)-**147**: monoclinic, space group $P2_1$ (no. 4), a = 9.83139(7) Å, b = 12.10798(10) Å, c = 18.33461(15) Å, β = 95.0265(7)°, V = 2174.13(3) Å^3, Z = 4, T = 150.15 K, μ(Cu Kα) = 2.816 mm^{-1}, *Dcalc* = 1.306 g/mm^3, 16749 reflections measured

(8.762 ≤ 2Θ ≤ 156.042), 8992 unique (R_{int} = 0.0249) which were used in all calculations. The final R_1 was 0.0479 (I > 2σ(I)) and wR_2 was 0.1322 (all data).

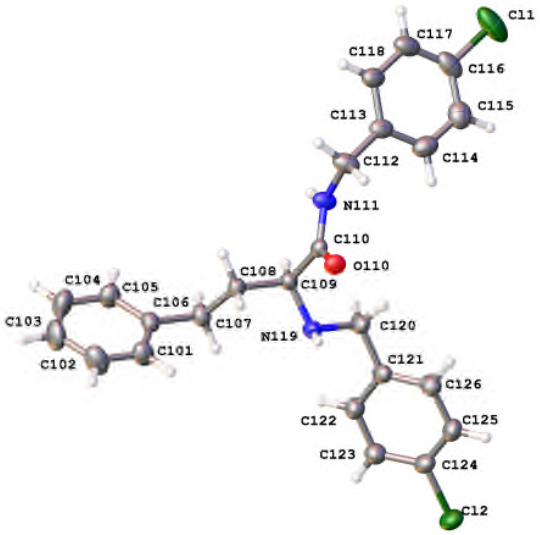
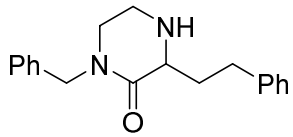


Figure 54 Solid state of one of (*S*)-**147** with atom labelling. Thermal ellipsoids are drawn at 50% probability.

The asymmetric unit contains two molecules of (*S*)-**147** and four in the unit cell. These two molecules are identical but differ only in rotations of the aromatic rings. The NHs of both the amines and the amides were located in a difference map and their positions were allowed to refine freely but give thermal parameters 1.5 times the U*iso* equivalent to the U*equiv* of the parent nitrogen (except H119 which was refined with a DFIX restraint). The Flack parameter refined to 0.022(14) by hole-in-one fit to all intensities and 0.023(10) from 3940 selected quotients (Parsons' method).[34] The Hooft y parameter refined to 0.025(4) (Olex2).[29]

5.3.12.4 Crystal Structure Determination of 158.



Single crystals of **158** were grown from ethyl acetate/hexane by M. W. M. Earl.[36] A suitable crystal was selected and mounted on a Mitigen Micromount using Fromblin oil

on an Oxford Diffraction Gemini Xcalibur diffractometer with a Ruby CCD area detector. The crystal was kept at 100(2) K during data collection. Using Olex2,[29] the structure was solved with the ShelXS[33] structure solution program using Direct Methods and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for **158**: orthorhombic, space group $Pca2_1$ (no. 29), a = 9.2888(2) Å, b = 6.04300(10) Å, c = 27.8317(6) Å, V = 1562.26(5) Å^3, Z = 4, T = 150.15 K, μ(Cu Kα) = 0.607 mm^{-1}, *Dcalc* = 1.252 g/mm^3, 7248 reflections measured ($6.352 \leq 2\Theta \leq 155.122$), 3120 unique ($R_{int}$ = 0.0273) which were used in all calculations. The final R_1 was 0.0309 ($I > 2\sigma(I)$) and wR_2 was 0.0833 (all data).

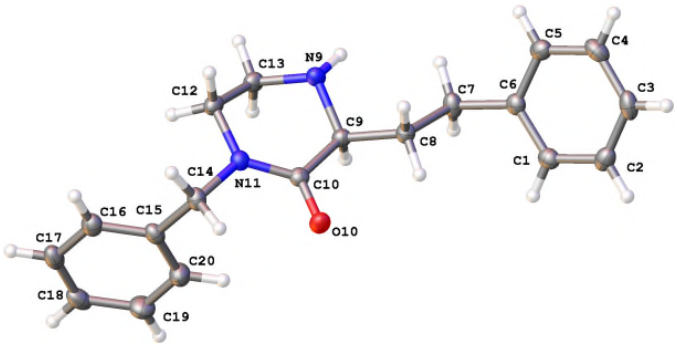
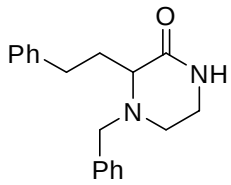


Figure 55 Solid state structure of **158** with atom labelling. Thermal ellipsoids are drawn at 50% probability.

The asymmetric unit contains 4 molecules of **158** in the unit cell (2 of each enantiomer). The molecule has crystallised in a polar space group so both enantiomers are present. Since the space group is polar it has a related Flack parameter which is 0.203(298) by hole-in-one fit to all intensities (Shelx 2013/14) and 0.015(132) from 1357 selected quotients (Parsons' method).[34] The Hooft y parameter refined to 0.07(12) (Olex2).[29] The NH was located in a difference map and allowed to refine freely but given a thermal parameter U*iso* equivalent to 1.5 times U*equiv* of the parent Nitrogen.

5.3.12.5 Crystal Structure Determination of 159.



Single crystals of **159** were grown from ethyl acetate/hexane. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Oxford Diffraction Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,[29] the structure was solved with the ShelXS[33] structure solution program using Direct Methods and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for **159**: triclinic, space group P-1 (no. 2), a = 5.3351(3) Å, b = 10.0384(5) Å, c = 15.6306(9) Å, α = 106.562(5)°, β = 98.033(5)°, γ = 95.518(4)°, V = 786.30(8) Å^3, Z = 2, T = 150(2) K, μ(CuKα) = 0.603 mm^{-1}, *Dcalc* = 1.243 g/mm^3, 5168 reflections measured (5.992 ≤ 2Θ ≤ 154.62), 3220 unique (R_{int} = 0.0200, R_{sigma} = 0.0252) which were used in all calculations. The final R_1 was 0.0420 (I > 2σ(I)) and wR_2 was 0.1183 (all data).

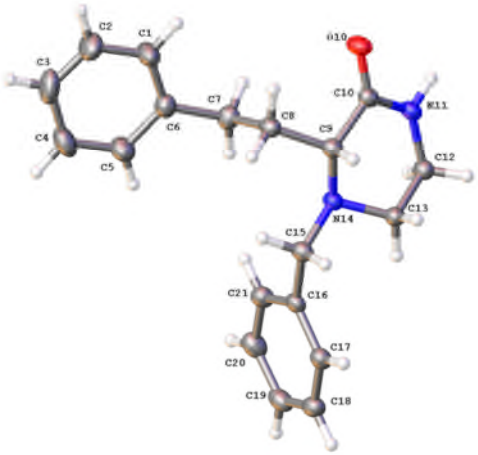
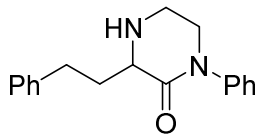


Figure 56 Solid state structure of **159** with atom labelling. Thermal ellipsoids are drawn at 50 % probability.

The disorder in the ring of the phenylethyl chain is removed for clarity. The asymmetric unit contains **159**. There are 2 molecules in the unit cell related by an inversion centre.

The ring of the phenylethyl chain was modeled as disordered over two positions by rotation about the C6-C7 bond (C3 and C6 belonged to both parts). The occupancies were refined to 47 : 53 (minor : major). The NH was located in a difference map and allowed to refine freely but given a thermal parameter Uiso 1.5 times the Uequiv of the parent nitrogen.

5.3.12.6 Crystal Structure Determination of 171.



Single crystals of **171** were grown from ethyl acetate/hexane. A suitable crystal was selected and mounted on a Mitegen loop with Fromblin oil on an Oxford Diffraction Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 100(2) K during data collection. Using Olex2,[29] the structure was solved with the ShelXS[33] structure solution program using Direct Methods and refined with the ShelXL[33] refinement package using Least Squares minimisation.

Crystal data for **171**: orthorhombic, space group $Pca2_1$ (no. 29), a = 27.3686(6) Å, b = 6.32664(13) Å, c = 8.74746(17) Å, V = 1514.63(6) Å^3, Z = 4, T = 150.15 K, μ(Cu Kα) = 0.602 mm^{-1}, *Dcalc* = 1.229 g/mm^3, 4385 reflections measured ($6.46 \leq 2\Theta \leq 133.174$), 2162 unique ($R_{int}$ = 0.0194) which were used in all calculations. The final R_1 was 0.0343 ($I > 2\sigma(I)$) and wR_2 was 0.0915 (all data).

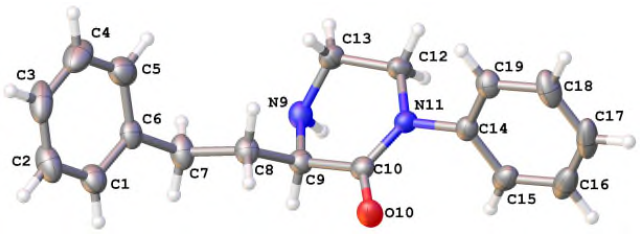


Figure 57 Solid state structure of **171** with atom labelling. Thermal ellipsoids are drawn at 50% probability.

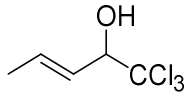
The asymmetric unit contains 4 molecules of **171** in the unit cell (2 of each enantiomer). The molecule has crystallised in a polar space group so both enantiomers are present. Since the space group is polar it has a related Flack parameter which is 0.2(2). The Hooft y parameter refined to 0.28(11) (Olex2).[29] The hydrogen on the amine was located in a difference map and was allowed to refine freely but given Uiso 1.5 times the Uequiv of the parent nitrogen.

5.4 EXPERIMENTAL FOR CHAPTER 3

5.4.1 Synthesis of Trichlorocarbinols.

Spectroscopic data for alcohols **25**, **40**, **43**, **44**, **46**, **47** and (*E*)-**49** were similar to that reported in **5.2.1. 207** was similar to that previously reported.[4]

(*E*)-1,1,1-Trichloropent-3-en-2-ol



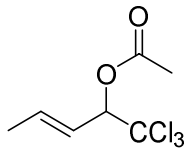
The title compound was synthesised using General Procedure 2 with (E)-but-2-enal (3.50 g, 50 mmol), trichloroacetic acid (12.25 g, 75 mmol), sodium trichloroacetate (13.90 g, 75 mmol) and DMF (67.5 mL). Residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a light yellow oil (5.53 g, 58 %).

δ_H (400 MHz; $CDCl_3$) 6.03 (1, dqd, *J* 15, 6.5 and 1, =C*H*COH), 5.67 (1H, ddq, *J* 15, 6.5 and 1.5, =C*H*CH_3), 4.51 (1H, t, *J* 6, C*H*OH), 2.93 (1H, d, *J* 6, O*H*), 1.80 (3H, ddd, *J* 6.5, 1.5 and 0.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 134.3 (=*C*HCOH), 125.0 (=*C*HCH_3), 102.9 (*C*Cl_3), 83.4 (*C*HOH), 18.0 (*C*H_3); GC-MS (EI) 171.2 ($C_5H_6{}^{35}Cl_3$, M-OH), 153.2 ($C_5H_7{}^{35}Cl_2O$, M-^{35}Cl), 135.2 ($[C_5H_5{}^{35}Cl_2]^+$, $[M-{}^{35}ClH_2O]^+$). It was not possible to obtain a HRMS (ESI) of this compound.

5.4.2 Synthesis of Racemic Acetates. General Procedure 11:

To a stirred solution of appropriate racemic trichlorocarbinol (26.8 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) at room temperature was added acetic anhydride (5.06 mL, 53.6 mmol, 2 equiv.) and pyridine (4.32 mL, 53.6 mmol, 2 equiv.). The reaction mixture was allowed to stir at room temperature for 17 hours. The residue was purified by silica column chromatography to afford product.

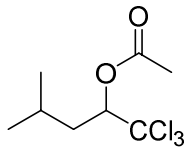
(*E*)-1,1,1-Trichloropent-3-en-2-yl acetate (*E*)-197.



The title compound was synthesised using General Procedure 11 with (*E*)-1,1,1-trichloropent-3-en-2-ol (*E*)-**109** (0.70 g, 3.74 mmol), acetic anhydride (0.71 mL, 7.48 mmol) and pyridine (0.98 mL, 7.48 mmol) in CH_2Cl_2 (20 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (0.36 g, 42 %).

ν_{max}/cm^{-1} (neat) 1757 (s, C=O st.), 1209 (s, C-O as. st.), 796 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 6.06 (1H, dq, *J* 15 and 6.5, C*H*=CHCH$_3$), 5.79 (1H, d, *J* 7.5, C*H*OAc), 5.62 (1H, ddq, *J* 15.5, 7.5 and 1.5, CH=C*H*CH$_3$), 2.17 (3H, s, CO*C*H$_3$), 1.80 (3H, dd, *J* 7.5 and 1.5, CH=CHC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.0 (*C*O), 136.5 (*C*H), 122.5 (*C*H), 99.1 (*C*Cl$_3$), 81.9 (C*H*OAc), 20.9 (CO*C*H$_3$), 18.0 (CH*C*H$_3$); GC-MS (EI) 195.2 ($C_7H_9{}^{35}Cl_2O_2$, M-^{35}Cl), 171.2 ([$C_5H_6{}^{35}Cl_3$]$^+$, [M-OCOCH$_3$]$^+$), 152.2 ([$C_5H_6{}^{35}Cl_2O$]$^+$, [M-^{35}ClCOCH$_3$]$^+$), 135.2 ([$C_5H_5{}^{35}Cl_2$]$^+$, M-^{35}ClHOCOCH$_3$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

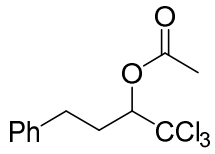
1,1,1-Trichloro-4-methylpentan-2-yl acetate 198.



The title compound was synthesised using General Procedure 11 with 1,1,1-trichloro-4-methylpentan-2-ol **44** (5.15 g, 26.8 mmol). The residue was purified by silica column chromatography (10 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (5.04 g, 76 %).

ν_{max}/cm^{-1} (neat) 1758 (s, C=O st.), 1208 (s, C-O as. st.), 767 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.61-5.54 (1H, m, C*H*OAc), 2.20 (3H, s, COC*H*$_3$), 1.90-1.82 (2H, m, C*H*$_2$CHOAc), 1.69-1.56 (1H, m, C*H*$(CH_3)_2$), 1.00-0.97 (6H, m, 2 x C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 169.7 (*C*O), 100.5 (*C*Cl_3), 79.4 (*C*HOAc), 39.4 (*C*H_2), 24.7 (*C*H$(CH_3)_2$), 23.5 (*C*H_3), 21.4 (*C*H_3), 20.8 (CO*C*H_3); GC-MS (EI) 231.2 ($[C_7H_{10}{}^{35}Cl_3O]^+$, $[M\text{-}CH_3]^+$), 211.2 ($[C_8H_{13}{}^{35}Cl_2O_2]^+$, $[M\text{-}{}^{35}Cl]^+$). It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichloro-4-phenylbutan-2-yl acetate 200.

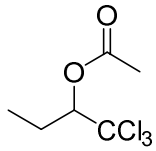


The title compound was synthesised using General Procedure 11 with 1,1,1-trichloro-4-phenylbutan-2-ol **25** (2.81 g, 11 mmol), acetic anhydride (2.08 mL, 22 mmol) and pyridine (1.78 mL, 22 mmol) in CH_2Cl_2 (30 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (3.11 g, 98 %).

ν_{max}/cm^{-1} (neat) 1756 (s, C=O st.), 1210 (s, C-O as. st.), 783 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.36-7.28 (2H, m, Ar*H*), 7.25-7.19 (3H, m, Ar*H*), 5.55 (1H, dd, *J* 10 and 2,

C*H*OAc), 2.77-2.66 (2H, m, C*H*$_2$Ph), 2.45 (1H, dddd, *J* 16, 9, 7 and 2, C*H*HCH$_2$Ph), 2.26-2.14 (4H, m, CH*H*CH$_2$Ph and COC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.7 (*C*O), 140.2 (Ar*C*$_{quat.}$), 128.6 (Ar*C*), 128.4 (Ar*C*), 126.4 (Ar*C*), 99.9 (*C*Cl_3), 80.5 (C*H*OAc), 32.2 (*C*H$_2$Ph), 31.8 (*C*H$_2$CH$_2$Ph), 20.7 (CO*C*H$_3$); GC-MS (EI) 216.2 ($[C_{10}H_{10}{}^{35}Cl_2O]^+$, [M-^{35}ClCCOCH$_3$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

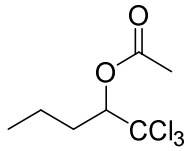
1,1,1-Trichlorobutan-2-yl acetate 201.



The title compound was synthesised using General Procedure 11 with 1,1,1-trichloro-4-butan-2-ol **207** (3.41 g, 19 mmol, 1 equiv.), acetic anhydride (3.77 mL, 38 mmol, 2 equiv.) and pyridine (3.22 mL, 38 mmol, 2 equiv.) in CH_2Cl_2 (40 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (1.30 g, 31 %).

ν_{max}/cm^{-1} (neat) 1757 (s, C=O st.), 1208 (s, C-O as. st.), 797 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.44 (1H, dd, *J* 10 and 2.5, C*H*OAc), 2.30-2.13 (4H, m, CHC*H*H and COC*H*$_3$), 1.84 (1H, ddq, *J* 14.5, 10 and 7.5, CHCH*H*), 1.00 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.9 (*C*O), 100.0 (*C*Cl_3), 82.1 (*C*HOAc), 23.7 (*C*H$_2$CH$_3$), 20.7 (CO*C*H$_3$), 10.0 (CH$_2$*C*H$_3$); GC-MS (EI) 217.8 ($C_6H_9{}^{35}Cl_3O_2$, M), 203.1 ($[C_5H_6{}^{35}Cl_3O_2]^+$, [M-CH$_3$]$^+$), 183.2 ($[C_6H_9{}^{35}Cl_2O_2]^+$, [M-^{35}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

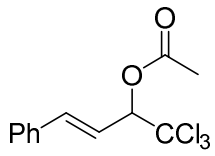
1,1,1-Trichloropentan-2-yl acetate 199.



The title compound was synthesised using General Procedure 11 with 1,1,1-trichloro-4-pentan-2-ol **40** (4.00 g, 22 mmol), acetic anhydride (4.15 mL, 44 mmol) and pyridine (3.54 mL, 44 mmol) in CH_2Cl_2 (40 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (3.78 g, 74 %).

ν_{max}/cm^{-1} (neat) 1757 (s, C=O st.), 1209 (s, C-O as. st.), 775 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.48 (1H, dd, *J* 10.5 and 2, C*H*OAc), 2.18 (1H, s, COC*H*$_3$), 2.07 (1H, dddd, *J* 14, 9.5, 7 and 2, C*H*HCHOAc), 1.82 (1H, dddd, *J* 14.5, 10, 9.5 and 5, CH*H*CHOAc), 1.49-1.30 (2H, m, C*H*$_2$CH$_3$), 0.97 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.8 (*C*O), 100.1 (*C*Cl_3), 80.6 (*C*HOAc), 32.4 (*C*H$_2$CHOAc), 20.7 (CO*C*H$_3$), 18.8 (*C*H$_2$CH$_3$), 13.6 (CH$_2$*C*H$_3$); GC-MS (EI) 197.1 ([$C_7H_{11}{}^{35}Cl_2O_2$]$^+$, [M-^{35}Cl]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

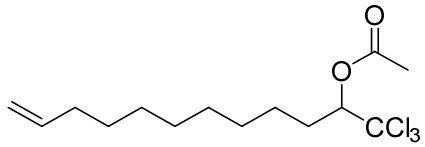
(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-yl acetate (*E*)-202.



The title compound was synthesised using General Procedure 11 with (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol (*E*)-**49** (6.65 g, 26.4 mmol), acetic anhydride (5.00 mL, 52.8 mmol) and pyridine (4.30 mL, 52.8 mmol) in CH_2Cl_2 (50 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to give a colourless oil (3.26 g, 42 %).

ν_{max}/cm^{-1} (neat) 1749 (s, C=O st.), 1207 (s, C-O as. st.), 783 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 7.50-7.41 (2H, m, Ar*H*), 7.40-7.29 (3H, m, Ar*H*), 6.89 (1H, d, *J* 16, CH=C*H*Ph), 6.30 (1H, dd, 16 and 7.5, C*H*=CHPh), 3.01 (1H, d, *J* 7.5, C*H*OAc), 2.22 (3H, s, COC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.0 (*C*O), 138.8 (=*C*HPh), 135.2 (Ar$C_{quat.}$), 128.9 (Ar*C*), 128.7 (Ar*C*), 127.0 (Ar*C*), 119.9 (*C*H=CHPh), 98.9 (*C*Cl_3), 82.0 (*C*HOAc), 20.9 (CO*C*H_3); GC-MS (EI) 233.2 ($C_{10}H_8{}^{35}Cl_3$, M-OCOCH$_3$), 214.4 ($[C_{10}H_8{}^{35}Cl_2O]^+$, [M-^{35}ClCOCH$_3$]$^+$). It was not possible to obtain a HRMS (ESI) of this compound.

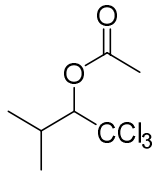
1,1,1-Trichlorodec-9-en-2-yl acetate 203.



The title compound was synthesised using General Procedure 11 with 1,1,1-trichlorodec-9-en-2-yl acetate **43** (5.18 g, 18.6 mmol), acetic anhydride (3.51 mL, 37.2 mmol) and pyridine (3.00 mL, 37.2 mmol) in CH_2Cl_2 (40 mL). The residue was used without any further purification to give a light yellow oil (4.14 g, 96 %).

ν_{max}/cm^{-1} (neat) 1759 (s, C=O st.), 1210 (s, C-O as. st.), 780 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.81 (1H, ddt, *J* 17, 10 and 6.5, C*H*=CH_2), 5.49 (1H, dd, *J* 10 and 2, C*H*OAc), 5.02-4.96 (1H, m, CH=CH_{trans}H), 4.94-4.91 (1H, m, CH=CHH_{cis}), 2.18 (3H, s, CH_3), 2.17-2.06 (1H, m, C*H*HCHOAc), 2.02 (2H, q, *J* 7, CH_2CH=CH_2), 1.81 (1H, ddt, *J* 14, 10 and 6.5, CH*H*CHOAc), 1.36-1.28 (12H, m, 6 x CH_2); δ_C (100 MHz; $CDCl_3$) 169.8 (*C*O), 139.1 (*C*H=CH_2), 114.1 (*C*H_2=CH), 100.2 (*C*Cl_3), 80.8 (*C*HOAc), 33.8 (*C*H_2), 30.3 (*C*H_2), 29.3 (*C*H_2), 29.2 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 28.8 (*C*H_2), 25.4 (*C*H_2), 20.7 (*C*H_3); GC-MS (EI) 328.5 ($[C_{14}H_{23}{}^{35}Cl_3O_2]^+$, $[M]^+$). It was not possible to obtain a HRMS (ESI) of this compound.

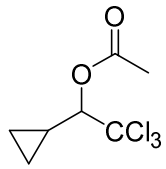
1,1,1-Trichloro-3-methylbutan-2-yl acetate 204.



The title compound was synthesised using General Procedure 11 with 1,1,1-trichloro-3-methylbutan-2-ol **46** (2.70 g, 15 mmol), acetic anhydride (2.83 mL, 30 mmol) and pyridine (2.42 mL, 30 mmol) in CH_2Cl_2 (35 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to afford a colourless oil (2.10 g, 60 %).

ν_{max}/cm^{-1} (neat) 1756 (s, C=O st.), 1210 (s, C-O as. st.), 794 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 5.33 (1H, d, *J* 3.5, C*H*OAc), 2.50 (1H, sept. d, *J* 7 and 3.5, C*H*$(CH_3)_2$), 2.19 (3H, s, COC*H*$_3$), 1.09 (3H, d, *J* 7, CH(C*H*$_3$)CH_3), 1.03 (3H, d, *J* 7, CH(CH_3)C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.7 (*C*O), 99.9 (*C*Cl_3), 84.0 (*C*HOAc), 30.1 (*C*H$(CH_3)_2$), 22.3 (CH(*C*H_3)CH_3), 20.5 (CO*C*H_3), 17.4 (CH(CH_3)*C*H_3); GC-MS (EI) 197.1 ($[C_7H_{11}{}^{35}Cl_2O_2]^+$, $[M-{}^{35}Cl]^+$). It was not possible to obtain a HRMS (ESI) of this compound.

1,1,1-Trichlorocyclopropylethan-2-yl acetate 205.



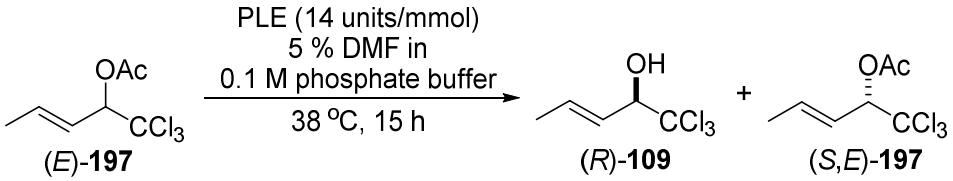
The title compound was synthesised using General Procedure 11 with 1,1,1-trichlorocyclopropylethan-2-ol **47** (3.88 g, 22.4 mmol), acetic anhydride (4.23 mL, 44.8 mmol) and pyridine (3.61 mL, 44.8 mmol) in CH_2Cl_2 (40 mL). The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to afford a colourless oil (2.60 g, 51 %).

ν_{max}/cm^{-1} (neat) 1758 (s, C=O st.), 1414 (s, C-O as. st.), 796 (s, C-Cl st.); δ_H (400 MHz; $CDCl_3$) 4.95 (1H, d, *J* 8.5, C*H*OAc), 2.18 (3H, s, COCH_3), 1.38 (1H, dtt, *J* 8.5, 8 and 5, C*H*CHOAc), 0.73-0.67 (1H, m, C$H_{cyclopropyl}$), 0.89-0.82 (1H, m, C$H_{cyclopropyl}$), 0.65-0.59 (1H, m, C$H_{cyclopropyl}$), 0.56 (1H, ddt, *J* 9.5, 6.5 and 5, C$H_{cyclopropyl}$); δ_C (100 MHz; $CDCl_3$) 169.6 (*C*O), 100.0 (*C*Cl_3), 84.3 (CHOAc), 20.8 (CO*C*H_3), 12.1 (*C*HCHCOAc), 6.2 (*C*H_2), 2.3 (*C*H_2); GC-MS (EI) 195.2 ($[C_7H_9{}^{35}Cl_2O_2]^+$, $[M-{}^{35}Cl]^+$). It was not possible to obtain a HRMS (ESI) of this compound.

5.4.3 Enzymatic Resolutions. General Procedure 12.

To a solution of the appropriate racemic acetate (0.5 mmol) in 5 or 10 % organic solvent in 0.1 M phosphate buffer (total volume = 8 mL) at 38 ºC was added the relevant enzyme. The resulting suspension was stirred at 38 ºC for 15 hours. To the reaction mixture was added CH_2Cl_2 (10 mL), which was then washed with distilled water (2 x 10 mL) and sat. aq. sodium chloride (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. This residue was used to acquire the ^{1}H NMR spectrum (for conversion) and GC/HPLC trace (for enantiomeric excesses).

(*R*,*E*)-1,1,1-Trichloropent-3-en-2-ol (*R*,*E*)-109 and (*S*,E)-1,1,1-trichloropent-3-en-2-yl acetate (*S*,*E*)-197.



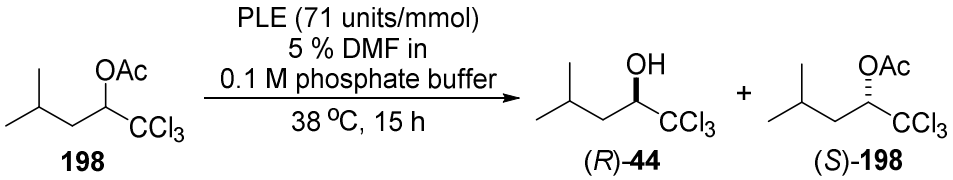
(*E*)-**197** (*R*)-**109** (*S*,*E*)-**197**

Enzymatic hydrolysis of (*E*)-1,1,1-trichloropent-3-en-2-yl acetate (*E*)-**197** (312 mg, 1.35 mmol) was performed using General Procedure 12 using PLE (1 mg, 19 units, 14 units/mmol) in DMF (0.35 mL) and 0.1 M phosphate buffer (7.35 mL) to give (*R*,*E*)-

1,1,1-trichloropent-3-en-2-ol and (*S*,*E*)-1,1,1-trichloropent-3-en-2-yl acetate in a 44 : 56 ratio, in 96 % e.e. and 60 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*R*)-**197** 31.4 min., (*S*)-**197** 31.8 min., (*S*)-**109** 69.3 min., (*R*)-**109** 71.8 min.

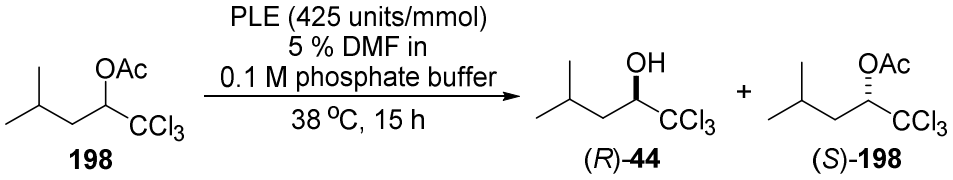
(*R*)-1,1,1-Trichloro-4-methylpentan-2-ol (*R*)-44 and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-198.



198 (*R*)-**44** (*S*)-**198**

Enzymatic hydrolysis of 1,1,1-trichloro-4-methylpentan-2-yl acetate **198** (936 mg, 4 mmol) was performed using General Procedure 12 using PLE (15 mg, 284 units, 71 units/mmol) in DMF (4 mL) and 0.1 M phosphate buffer (47.5 mL) to give (*R*)-1,1,1-trichloro-4-methylpentan-2-ol (*R*)-**44** and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-**198** in a 47 : 53 ratio, in 97 % e.e. and 79 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*S*)-**198** 36.7 min., (*R*)-**198** 38.1 min., (*S*)-**44** 68.0 min., (*R*)-**44** 77.7 min.

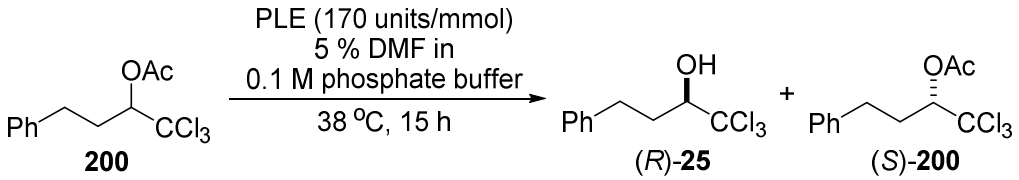


198 (*R*)-**44** (*S*)-**198**

Enzymatic hydrolysis of 1,1,1-trichloro-4-methylpentan-2-yl acetate **198** (100 mg, 0.4 mmol) was performed using General Procedure 12 using PLE (10 mg, 170 units, 425 units/mmol) in DMF (0.25 mL) and 0.1 M phosphate buffer (4.75 mL) to give (*R*)-1,1,1-trichloro-4-methylpentan-2-ol (*R*)-**44** and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-**198** in a 62 : 38 ratio, in 78 % e.e. and > 99 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*R*)-**198** 37.5 min., (*S*)-**44** 68.4 min., (*R*)-**44** 79.6 min.

(*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*R*)-25 and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-200.

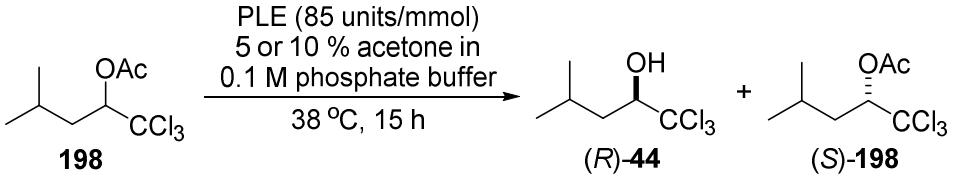


Enzymatic hydrolysis of 1,1,1-trichloro-4-phenylbutan-2-yl acetate **200** (147 mg, 0.5 mmol) was performed using General Procedure 12 using PLE (5 mg, 85 units, 170 units/mmol) in DMF (0.8 mL) and 0.1 M phosphate buffer (7.2 mL) to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 34 : 66 ratio, in 29 % e.e. and 11 % e.e. respectively.

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 10.45 min., (*S*)-**200** 12.21 min., (*S*)-**25** 26.93 min., (*R*)-**25** 48.21 min.).

5.4.3.1 Enzymatic resolutions in acetone.

(*R*)-1,1,1-Trichloro-4-methylpentan-2-ol (*R*)-44 and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-198.



Enzymatic hydrolysis of 1,1,1-trichloro-4-methylpentan-2-yl acetate **198** (124 mg, 0.5 mmol) was performed using General Procedure 12 using PLE (2.5 mg, 42.5 units, 85 units/mmol) in:

(Table 10, entry 1) 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-methylpentan-2-ol (*R*)-**44** and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-**198** in a 53 : 47 ratio, in 98 % e.e. and 95 % e.e. respectively.

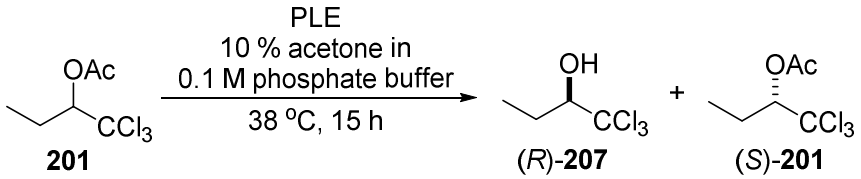
Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*S*)-**198** 36.4 min., (*R*)-**198** 37.9 min., (*S*)-**44** 67.3 min., (*R*)-**44** 76.2 min.

and

(Table 10, entry 2) 20 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-methylpentan-2-ol (*R*)-**44** and (*S*)-1,1,1-trichloro-4-methylpentan-2-yl acetate (*S*)-**198** in a 29 : 71 ratio, in 98 % e.e. and 37 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*S*)-**198** 36.4 min., (*R*)-**198** 37.6 min., (*S*)-**44** 67.5 min., (*R*)-**44** 77.4 min.

(*R*)-1,1,1-Trichlorobutan-2-ol (*R*)-207 and (*S*)-1,1,1-trichlorobutan-2-yl acetate (*S*)-201.



201 (*R*)-**207** (*S*)-**201**

Enzymatic hydrolysis of 1,1,1-trichlorobutan-2-yl acetate **201** (124 mg, 0.5 mmol) was performed using General Procedure 12 with 10 % acetone in 0.1 M phosphate buffer using:

(Table 10, entry 3) PLE (1 mg, 17 units, 34 units/mmol) to give (*R*)-1,1,1-trichlorobutan-2-ol (*R*)-**207** and (*S*)-1,1,1-trichlorobutan-2-yl acetate (*S*)-**201** in a 11 : 89 ratio, in 93 % e.e. and 13 % e.e. respectively.

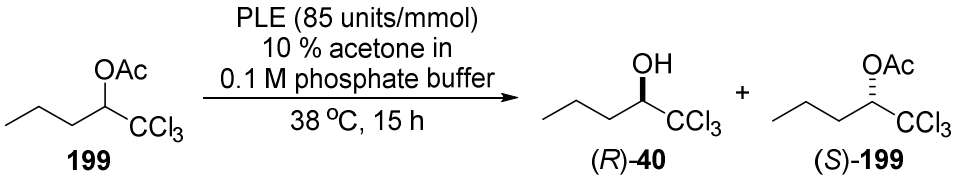
Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 95 °C, P = 15 psi (H_2 gas) (*S*)-**201** 25.9 min., (*R*)-**201** 26.9 min., (*S*)-**207** 39.6 min., (*R*)-**207** 42.6 min.

and

(Table 10, entry 4) PLE (2.5 mg, 42.5 units, 85 units/mmol) to give (*R*)-1,1,1-trichlorobutan-2-ol (*R*)-**207** and (*S*)-1,1,1-trichlorobutan-2-yl acetate (*S*)-**201** in a 27 : 73 ratio, in 88 % e.e. and 30 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 95 °C, P = 15 psi (H_2 gas) (*S*)-**201** 26.0 min., (*R*)-**201** 27.0 min., (*S*)-**207** 39.5 min., (*R*)-**207** 42.3 min.

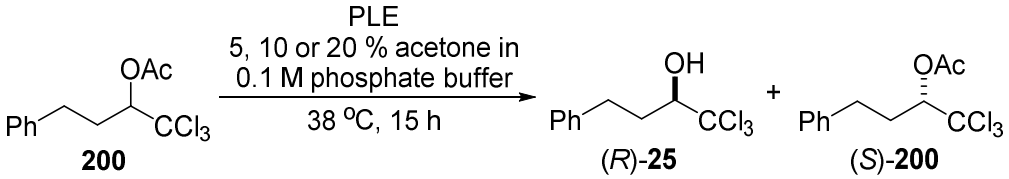
(*R*)-1,1,1-Trichloropentan-2-ol (*R*)-40 and (*S*)- 1,1,1-trichloropentan-2-yl acetate (*S*)-199.



Enzymatic hydrolysis of 1,1,1-trichloropentan-2-yl acetate **199** (147 mg, 0.5 mmol) was performed using General Procedure 2 using PLE (2.5 mg, 42.5 units, 85 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloropentan-2-ol (*R*)-**40** and (*S*)-1,1,1-trichloropentan-2-yl acetate (*S*)-**199** in a 46 : 54 ratio, in 96 % e.e. and 73 % e.e. respectively (Table 10, entry 5).

Chiral HPLC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 100 °C, P = 15 psi (H_2 gas) (*S*)-**199** 30.8 min., (*R*)-**199** 31.6 min., (*S*)-**40** 50.1 min., (*R*)-**40** 54.8 min.

(*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*R*)-25 and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-200.



Enzymatic hydrolysis of 1,1,1-trichloro-4-phenylbutan-2-yl acetate **200** (147 mg, 0.5 mmol) was performed using General Procedure 12 using:

(Table 10, entry 6) PLE (1 mg, 17 units, 34 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 34 : 66 ratio, in 71 % e.e. and 39 % e.e. respectively.

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 10.83 min., (*S*)-**200** 12.71 min., (*S*)-**25** 28.40 min., (*R*)-**25** 49.98 min.

and

(Table 10, entry 7) PLE (2.5 mg, 42.5 units, 85 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 40 : 60 ratio, in 77 % e.e. and 41 % e.e. respectively.

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 10.84 min., (*S*)-**200** 12.79 min., (*S*)-**25** 29.06 min., (*R*)-**25** 51.64 min.

and

(Table 10, entry 8) PLE (2.5 mg, 42.5 units, 85 units/mmol) with 5 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 37 : 63 ratio, in 72 % e.e. and 36 % e.e. respectively.

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 9.73 min., (*S*)-**200** 11.25 min., (*S*)-**25** 23.16 min., (*R*)-**25** 39.46 min.

and

(Table 10, entry 9) PLE (10 mg, 170 units, 340 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 56 : 44 ratio, in 53 % e.e. and 76 % e.e. respectively.

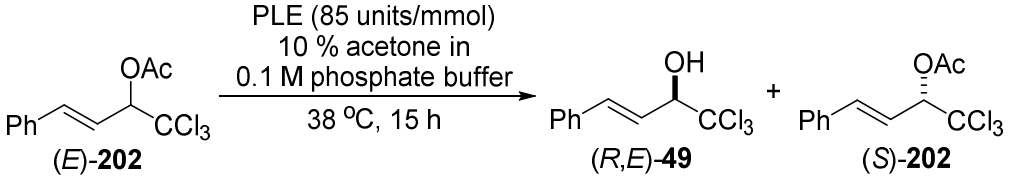
Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 10.84 min., (*S*)-**200** 12.76 min., (*S*)-**25** 28.82 min., (*R*)-**25** 49.48 min.

and

(Table 10, entry 10) PLE (10 mg, 170 units, 340 units/mmol) with 20 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichloro-4-phenylbutan-2-ol (*R*)-**25** and (*S*)-1,1,1-trichloro-4-phenylbutan-2-yl acetate (*S*)-**200** in a 63 : 37 ratio, in 69 % e.e. and 82 % e.e. respectively.

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 0.5 mL/min., 209 nm, (*R*)-**200** 10.45 min., (*S*)-**200** 12.21 min., (*S*)-**25** 25.93 min., (*R*)-**25** 44.68 min.

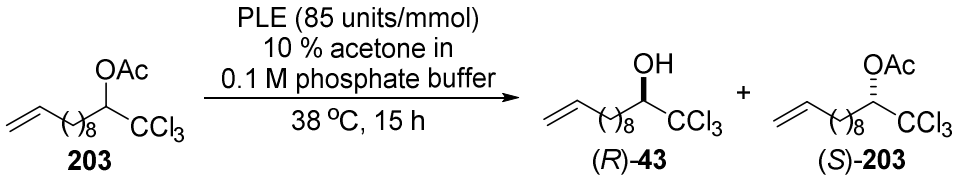
(*R*,*E*)-1,1,1-Ttrichloro-4-phenylbut-3-en-2-ol (*R*,*E*)-49 and (*S*,*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-yl acetate (*S*,*E*)-202.



Enzymatic hydrolysis of (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-yl acetate (*E*)-**202** (146 mg, 0.5 mmol) was performed using General Procedure 12 using PLE (2.5 mg, 42.5 units, 85 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*,*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol (*R*,*E*)-**49** and (*S*,*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-yl acetate (*S*,*E*)-**202** in a 10 : 90 ratio, with (*R*,*E*)-**49** in 86 % e.e. (Table 10, entry 11).

Chiral HPLC: Daicel Chiralcel OD-H column, 2-propanol : *n*-hexane = 5 : 95, 1 mL/min., 253 nm, (*S*,*E*)-**49** 29.24 min., (*R*,*E*)-**49** 30.88 min.

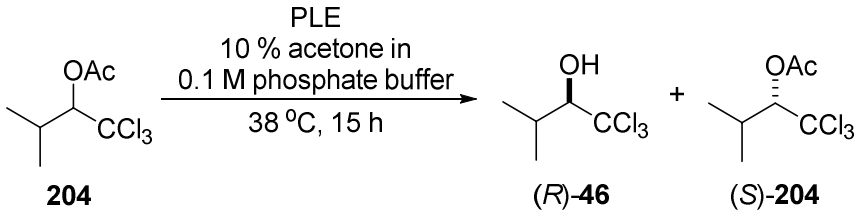
(*R*)-1,1,1-Trichlorododec-11-en-2-ol (*R*)-43 and (*S*)-1,1,1-trichlorododec-11-en-2-yl acetate (*S*)-203.



Enzymatic hydrolysis of 1,1,1-trichlorododec-11-en-2-yl acetate **203** (164 mg, 0.5 mmol) was performed using General Procedure 12 using PLE (2.5 mg, 42.5 units, 85 units/mmol) with 10 % acetone in 0.1 M phosphate buffer to give (*R*)-1,1,1-trichlorododec-11-en-2-ol (*R*)-**43** and (*S*)-1,1,1-trichlorododec-11-en-2-yl acetate (*S*)-**203** in a 42 : 58 ratio, in 59 % e.e. and 36 % e.e. respectively (Table 10, entry 12).

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 160 °C, P = 15 psi (H_2 gas) (*S*)-**203** 73.4 min., (*R*)-**203** 74.4 min., (*S*)-**43** 97.1 min., (*R*)-**43** 101.0 min.

(*R*)-1,1,1-Trichloro-3-methylbutan-2-ol (*R*)-46 and (*S*)- 1,1,1-trichloro-3-methylbutan-2-yl acetate (*S*)-204.



Enzymatic hydrolysis of 1,1,1-trichloro-3-methylbutan-2-yl acetate **204** (117 mg, 0.5 mmol) was performed using General Procedure 12 with 10 % acetone in 0.1 M phosphate buffer using:

(Table 10, entry 13) PLE (2.5 mg, 42.5 units, 85 units/mmol) to give (*R*)-1,1,1-trichloro-3-methylbutan-2-ol (*R*)-**46** and (*S*)- 1,1,1-trichloro-3-methylbutan-2-yl acetate (*S*)-**204** in a 15 : 85 ratio, in 91 % e.e. and 14 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**204** 12.9 min., (*R*)-**204** 13.3 min., (*S*)-**46** 19.1 min., (*R*)-**46** 19.7 min.

and

(Table 10, entry 14) PLE (5 mg, 85 units, 170 units/mmol) to give (*R*)-1,1,1-trichloro-3-methylbutan-2-ol (*R*)-**46** and (*S*)- 1,1,1-trichloro-3-methylbutan-2-yl acetate (*S*)-**204** in a 32 : 68 ratio, in 85 % e.e. and 35 % e.e. respectively.

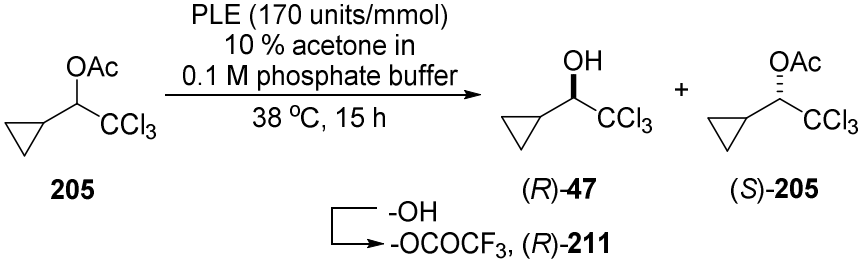
Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**204** 13.0 min., (*R*)-**204** 13.3 min., (*S*)-**46** 19.0 min., (*R*)-**46** 19.7 min.

and

(Table 10, entry 15) PLE (10 mg, 170 units, 340 units/mmol) to give (*R*)-1,1,1-trichloro-3-methylbutan-2-ol (*R*)-**46** and (*S*)- 1,1,1-trichloro-3-methylbutan-2-yl acetate (*S*)-**204** in a 44 : 56 ratio, in 81 % e.e. and 56 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**204** 12.9 min., (*R*)-**204** 13.2 min., (*S*)-**46** 18.8 min., (*R*)-**46** 19.3 min.

(*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-47 and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-205.

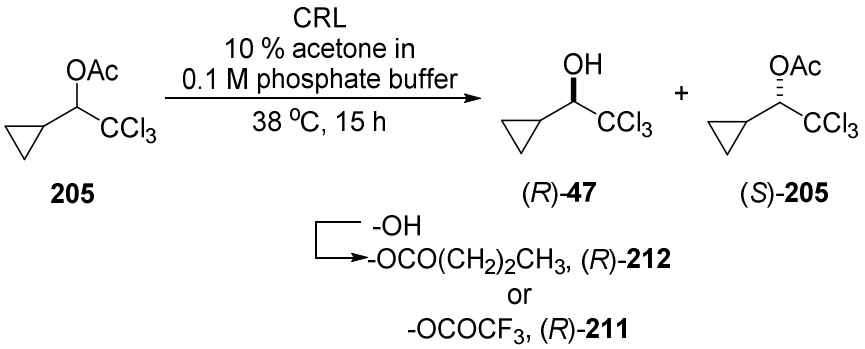


Enzymatic hydrolysis of 2,2,2-trichloro-1-cyclopropylethyl acetate **205** (116 mg, 0.5 mmol) was performed using General Procedure 12 using PLE (5 mg, 85 units, 170 units/mmol) with 10 % acetone in 0.1 M phosphate buffer using to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 74 : 26 ratio, in 68 % e.e. and 84 % e.e. respectively (Table 10, entry 16).

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 95 °C, P = 15 psi (H_2 gas) (*S*)-**211** 26.2 min., (*R*)-**211** 27.1 min., (*S*)-**205** 39.2 min., (*R*)-**205** 41.8 min.

5.4.3.2 Enzymatic resolutions with Candida rugosa lipase (CRL).

(*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-47 and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-205.



Enzymatic hydrolysis of 2,2,2-trichloro-1-cyclopropylethyl acetate **205** (116 mg, 0.5 mmol) was performed using General Procedure 12 with 10 % acetone in 0.1 M phosphate buffer using:

(Table 11, Entry 1) CRL (20 mg, 18,860 units, 37,720 units/mmol, Sigma Aldrich) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 15 : 85 ratio, in 94 % e.e. and 85 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 95 °C, P = 15 psi (H_2 gas) (*S*)-**211** 12.6 min., (*R*)-**211** 13.0 min., (*S*)-**205** 42.6 min., (*R*)-**205** 44.2 min.

and

(Table 11, Entry 2) CRL (50 mg, 47,150 units, 94,300 units/mmol, Sigma Aldrich) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 27 : 73 ratio, in 96 % e.e. and 37 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**205** 18.7 min., (*R*)-**205** 19.1 min., (*S*)-**212** 42.9 min., (*R*)-**212** 43.5 min.

and

(Table 11, Entry 3) CRL (80 mg, 75,440 units, 150,880 units/mmol, Sigma Aldrich) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 37 : 63 ratio, in 94 % e.e. and 24 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**205** 18.7 min., (*R*)-**205** 19.2 min., (*S*)-**212** 42.9 min., (*R*)-**212** 43.5 min.

and

(Table 11, Entry 4) CRL (50 mg, 115 units, 230 units/mmol, Fluka) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 20 : 80 ratio, in 97 % e.e. and 23 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**205** 18.7 min., (*R*)-**205** 19.1 min., (*S*)-**212** 42.9 min., (*R*)-**212** 43.5 min.

and

(Table 11, Entry 5) CRL (50 mg, 650 units, 1,300 units/mmol, Fluka, Sol-Gel) showed no reactivity.

and

(Table 11, Entry 6) CRL (55 mg, 7,185 units, 14,370 units/mmol, Biocatalysts Ltd) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 32 : 68 ratio, in 97 % e.e. and 31 % e.e. respectively.

Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**205** 18.7 min., (*R*)-**205** 19.2 min., (*S*)-**212** 42.9 min., (*R*)-**212** 43.5 min.

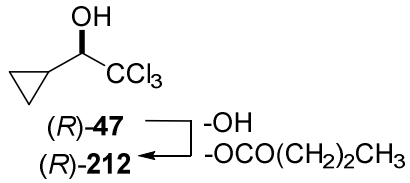
and

(Scheme 160) CRL (80 mg, 10,440 units, 20,880 units/mmol, Biocatalysts Ltd) to give (*R*)-2,2,2-trichloro-1-cyclopropylethan-1-ol (*R*)-**47** and (*S*)-2,2,2-trichloro-1-cyclopropylethyl acetate (*S*)-**205** in a 68 : 32 ratio, in 32 % e.e. and 97 % e.e. respectively.

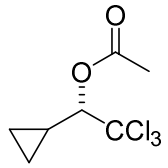
Chiral GC: CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas) (*S*)-**205** 18.7 min., (*R*)-**205** 19.2 min., (*S*)-**212** 42.8 min., (*R*)-**212** 43.3 min.

5.4.3.3 Synthesis, and isolation, of (*R*)-47 and (*S*)-205 using CRL.

To 1,1,1-trichlorocyclopropylethan-2-yl acetate **205** (984 mg, 4.25 mmol) in acetone (6.8 mL) and 0.1 M phosphate buffer (61.2 mL) at 38 ºC was added CRL (468 mg, 61,074 units, 14,370 units/mmol, Biocatalysts Ltd). The resulting suspension was stirred at 38 ºC for 15 hours. The reaction mixture was washed with distilled water (2 x 40 mL) and sat. aq. sodium chloride (40 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The ^{1}H NMR of the crude mixture showed a conversion of 32 % to (*R*)-**47**. The residue was purified by silica column chromatography (5 % ethyl acetate in 40-60 petroleum ether) to afford (*R*)-**47** as a colourless oil (175 mg, 15 %, 97 % e.e.) and (*S*)-**205** as a colourless oil (368 mg, 37 %, 40 % e.e.).



Spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (*c* 0.55, MeOH): + 7.7; Enantiomeric excess determined by GC analysis on butyl acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas), (*S*)-**212** 42.9 min., (*R*)-**212** 43.2 min.).



(*S*)-**205**

Spectroscopic data similar to that of racemate; Enantiomeric excess determined by GC analysis on butyl acetate derivative of product (CP-cyclodextrin-β-2,3,6-M-19, 50m 0.25mm 0.25μm, T = 120 °C, P = 15 psi (H_2 gas), (*S*)-**205** 18.5 min., (*R*)-**205** 19.0 min.).

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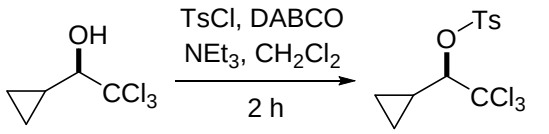
APPENDIX 1

This work was completed after the initial submission of this thesis.

X-ray crystal structure of (*R*)-2,2,2-trichloro-1-cyclopropylethyl 4-methylbenzenesulfonate:

Synthesis:

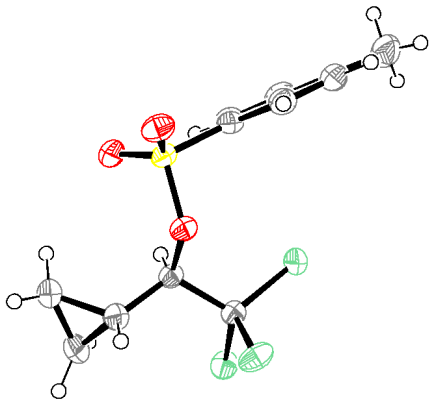


(*R*)-**47**
97 % e.e.

78 %, 98 % e.e.

Procedure taken from P. N. Confalone *et al*., *J. Org. Chem.* 2000, **65**, 1889-1891

X-ray:



Thermal ellipsoids drawn at 50 % probability

Single crystals of (*R*)-2,2,2-trichloro-1-cyclopropylethyl 4-methylbenzenesulfonate were grown from ethyl acetate/hexane. A suitable crystal was selected and mounted on a glass fibre and placed on an Oxford Diffraction Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,[1] the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[2] refinement package using Least Squares minimisation.

Crystal Data for (*R*)-2,2,2-trichloro-1-cyclopropylethyl 4-methylbenzenesulfonate:

monoclinic, space group $P2_1$ (no. 4), a = 5.91400(10) Å, b = 16.6340(2) Å, c = 8.12460(10) Å, β = 110.889(2)°, V = 746.71(2) Å^3, Z = 2, T = 150(2) K, μ(CuKα) = 6.881 mm^{-1}, *Dcalc* = 1.528 g/cm^3, 12415 reflections measured (10.636° ≤ 2Θ ≤ 156.164°), 3158 unique (R_{int} = 0.0369, R_{sigma} = 0.0273) which were used in all calculations. The final R_1 was 0.0281 (I > 2σ(I)) and wR_2 was 0.0745 (all data).

The asymmetric unit contains the molecule, there are two molecules in the unit cell. The Flack parameter is 0.002(13).

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